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National Institute of Infectious Diseases and
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Control Division,
Ministry of Health, Labour and Welfare

<THE TOPIC OF THIS MONTH>
Enterovirus infections in association with aseptic meningitis in Japan, as of December 2008

Japan has experienced outbreaks of aseptic meningitis in every summer. Echoviruses (E), group B coxsackieviruses (CB) and other enteroviruses occupied 80-90% of the causative agents (Fig. 4). Their prevalent serotypes changed from year to year. Regional variation in the prevalent types has been noted. Prognosis of aseptic meningitis caused by the enteroviruses is generally good, and acute encephalitis is rather rare. However, during the enterovirus 71 (EV71)-related hand, foot and mouth disease (HFMD) epidemic in the Asia-Pacific region, frequency of complications involving the central nervous system was elevated, and there were very severe or even fatal cases (see p. 9 of this issue).

Aseptic meningitis is a category V infectious disease under the Infectious Diseases Control Law enacted in April 1999. For the National Epidemiological Surveillance of Infectious Diseases (NESID) under the law, about 470 sentinel points are selected among hospitals with ≥300 beds providing care of the pediatrics and the internal medicine for weekly reporting of clinical aseptic meningitis cases. Prefectural and municipal public health institutes (PHIs) are responsible for isolation, identification and reporting of etiological agents from specimens (cerebrospinal fluids, stools, pharyngeal swabs, etc.) collected at sentinel points.

Incidence: Fig. 1 shows the weekly report of number of aseptic meningitis cases since April 1999. There was a large outbreak in 2002 and the cumulative patient number of the year was 2,985 (6.31 cases per sentinel). Since then, however, the scale of the epidemics has remained small. In the past 6-7 years, the incidence of the aseptic meningitis has been low (less than one case/sentinel/year) in Hokkaido, Iwate, Miyagi, Ibaraki, Yamaguchi and Kagawa Prefectures. Other prefectures have experienced outbreaks at one time or another but not simultaneously, indicating no nationwide epidemic has occurred in recent years (see Fig. 2 available at http://idsc.nih.go.jp/iasr/30/347/tpc347.html). The age distribution of cases has changed in recent years (Fig. 3). Until 2003, children under nine years old accounted for around 70% of the cases, but since 2006, cases over ten years old increased and they exceeded a half of the cases in 2008.

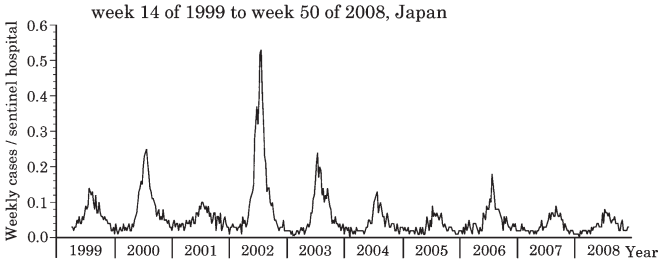
Isolation and detection of enteroviruses: In 2002, when aseptic meningitis surged, E13 was predominant, followed by E11, E30, E9 and CB2 (Table 1 on p. 3). In later years, the predominant types were E30, E6, EV71, E18 and E9 in 2003, E6, E30, CB5, CB1 and E18 in 2004, E9 and CB3 in 2005, E18, E30 and CB5 in 2006, CB5 and E30 in 2007, and E30 in 2008. Above listed are the types isolated each from more than 50 cases per year (Table 1 and Fig. 4).

Prevalence of each echovirus serotype or EV71 tends to recur with intervals of several years to decades. E13, unreported until 2000, was isolated abundantly from 2001 to 2002. It then declined during 2003-2006 and disappeared from the report since 2007. E30 caused large-scale nationwide outbreaks three times; in 1983 [IASR 4(10): 1, 1983], 1989-1991 (IASR 12: 163, 1991&13: 155, 1992) and 1997-1998 (IASR 19: 174-175, 1998). Then the epidemic pattern changed to yearly occurrence of local epidemics. In 2008, however, E30 aseptic meningitis broke out among high school students (see p. 8 of this issue). EV71 prevalence has recurred every three to four years, and the most recent one was in 2006.

In contrast to the recurrent echovirus prevalence, CB virus types 2-5 have been consistently isolated every year. A large number of CB5 cases were reported in 2007, and the reported number was the next to that in 1984.

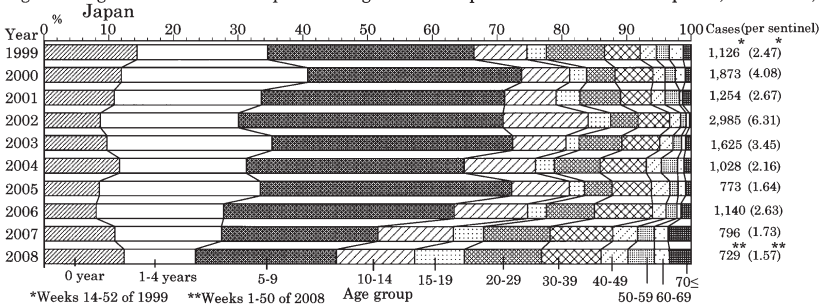
In 2006-2008, E30, E18 and CB5 were viruses most frequently isolated from aseptic meningitis cases. Fig. 5 shows the age distribution of the isolation sources of

Figure 1. Weekly cases of aseptic meningitis per sentinel hospital from week 14 of 1999 to week 50 of 2008, Japan



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before December 17, 2008)

Figure 3. Age distribution of aseptic meningitis cases reported from sentinel hospitals, 1999-2008, Japan



*Weeks 14-52 of 1999 **Weeks 1-50 of 2008

(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before December 17, 2008)

E30, E18, CB5 and EV71. While E30 and E18 were isolated/detected from a wide range of age groups, meningitis cases from which these viruses were isolated were among 0 year infants and among children over 3 years with the highest incidence peak at 5 years. For CB5, the virus isolation/detection was most frequent from 0-year infants and the isolation from children after school age has been rare. The peak of the CB5-associated aseptic meningitis was also at 0 year. EV71 was isolated/detected mostly from the young children with peak ages of 1-2 years. However, incidence of aseptic meningitis associated with EV71 had two peaks, one at 0-year and the other at 5-years.

E30, E18, CB5 and EV71 were isolated from various sources other than aseptic meningitis. E30 was isolated/ detected from the upper respiratory tract inflammation and infectious gastroenteritis, E18 from upper respiratory tract inflammation and fever of unknown origin (FOU), CB5 from infectious gastroenteritis and FOU, and EV71 from HFMD.

Figure 4. Isolation/detection of viruses from aseptic meningitis cases, 2003-2008, Japan
(Infectious Agents Surveillance Report: Data based on the reports received before December 16, 2008)

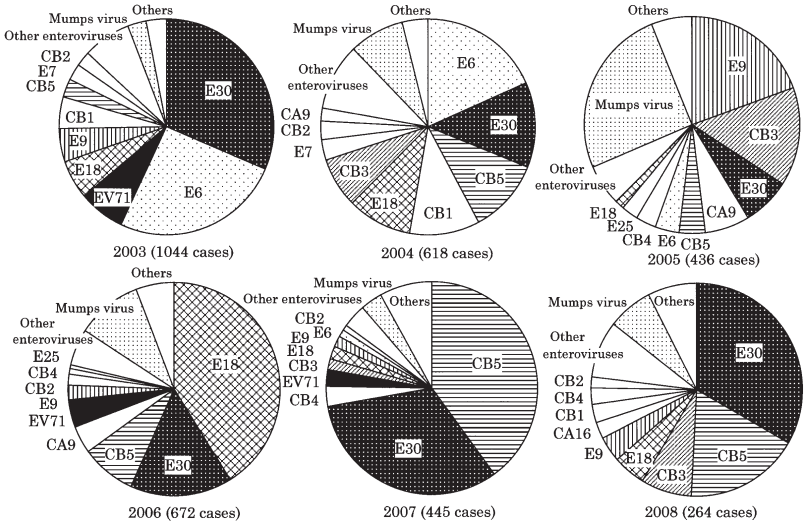
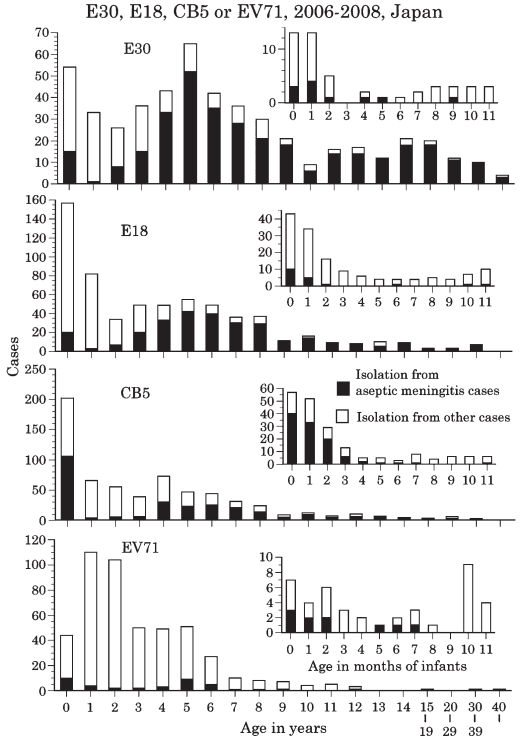


Figure 5. Age distribution of cases with isolation/detection of E30, E18, CB5 or EV71, 2006-2008, Japan



(Infectious Agents Surveillance Report: Data based on the reports received before December 16, 2008)

Table 2 on page 3 shows specimens from which enteroviruses were isolated or detected during 2006-2008. Compared with E30, E18 and CB5, EV71 was less frequently isolated/detected from the cerebrospinal fluids (see p. 10 of this issue).

Table 2 also shows isolation/detection methods applied to the enteroviruses identified during 2006-2008. Recent tendency is increasing application of PCR. Although PCR is useful for rapid diagnosis, attention must be paid to selecting primers, possible cross-contamination or other technical problems (see p. 4, 10&13 of this issue). The detection rate of enteroviruses from cerebrospinal fluids by PCR is higher than that by virus isolation in cultured cells or suckling mice (see p. 6 of this issue). PCR coupled with nucleotide sequencing is now increasingly available. However, certain important information is available only through virus isolation. Therefore, conventional virus isolation and identification should be conducted in parallel with the direct molecular detection (see p. 5 of this issue).

Other remarks: Sentinel surveillance of aseptic meningitis started in July 1981 with weekly reporting schedule until December 1986. It was switched to monthly reporting in January 1987 with expectation of collecting information on causative agents. It was continued till March 1999. However, expected information on causative agent(s) was rarely attached to the reports. In addition, monthly report delayed timely information sharing. Therefore, weekly reporting scheme was resumed in April 1999.

In the current weekly reporting system, only a small number of reports carry information on infectious agents. Namely, the current NESID needs further improvement.

From the start of NESID, sentinel hospitals were all designated as pathogen sentinels, i.e., responsible for collecting specimens for laboratory diagnosis (see above). It is advisable that the health centers request physicians in the sentinel hospitals to send specimens to PHIs for the microbiological diagnosis.

It may happen that non-sentinel hospitals or clinics detect a sign of meningitis outbreak. Even in such cases, the investigation using laboratory diagnosis should be considered as an active epidemiological investigation. When EV71 is detected during an epidemic of HFMD, attention is required for possible occurrence of severe neurological complications.

The Infectious Disease Surveillance Center, the National Institute of Infectious Diseases is providing the most recent trend of incidence and virus isolation/detection, which is uploaded on the URLs http://idsc.nih.go.jp/idwr/index-e.html and http://idsc.nih.go.jp/iasr/index.html. It will be useful information sources for physicians in charge of patient diagnosis and for organizations concerned.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Enteric Infection in Japan, have provided the above data.

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<THE TOPIC OF THIS MONTH>
Measles in Japan, 2008

According to the recent WHO announcement, the estimated number of deaths related to measles infection in the world was reduced from 750,000 in 2000 to 197,000 in 2007. In parallel, there was three-fold reduction in the reported number of patients in the same period (WHO, WER 83: 441-448, 2008). In the WHO Western Pacific Region including Japan, the current target year of measles elimination is 2012.

Japan formerly used the one dose measles vaccine for routine immunization to children 12-90 months after birth. In 2006, the vaccination schedule was revised and measles-rubella combined vaccine was introduced. Now the target age of the first vaccination is one year, and that of the second vaccination is one year preceding primary school entrance (5-6 years of age). Namely, two doses of measles-containing vaccine (MCV) are required before entrance to the primary school (IASR 27: 85-86, 2006). In addition, in 2007, in response to the outbreak of measles among young populations in their 10s and 20s (IASR 28: 239-240, 2007), vaccination to the first grade students of the junior high school (12-13 years of age) and those aged 17-18 years (including the third grade students of the high school) were added as five-year temporal measures under the Preventive Vaccination Law so as to increase the immunity level among this population.

The measles case reporting in compliance with the Infectious Diseases Control Law was also changed to notification of all cases in January 2008 (IASR 29: 179-181 & 189-190, 2008). In the former sentinel surveillance of measles, the sentinel clinics and hospitals reported clinically diagnosed cases since the National Epidemiological Surveillance of Infectious Diseases (NESID) started in July 1981. But, the doctors are now under an obligation of reporting measles cases together with clinical diagnosis and, where possible, laboratory data to the nearby health center. On account of their recent increase among the people received one dose of MCV, the "modified measles" cases that failed to exhibit the typical symptoms are requested to be reported if they are confirmed by the laboratory diagnosis (information of measles is found in http://idsc.nih.go.jp/disease/measles/index.html).

Measles incidence under the NESID: During weeks 1-52 of 2008, total 11,007 cases, 4,200 cases based on laboratory diagnosis (including 1,024 "modified" measles cases) and 6,807 cases based on clinical diagnosis, were reported (as of January 21, 2009). In 2008, measles increased suddenly in week 5 and maintained its high incidence level for more than 20 weeks. There were two peaks, one in week 7 (567 cases) and the other in week 17 (543 cases). It subsided gradually and became less than 50 cases after week 32, but more than 10 cases continued to be reported every week up to the week 52 (Fig. 1).

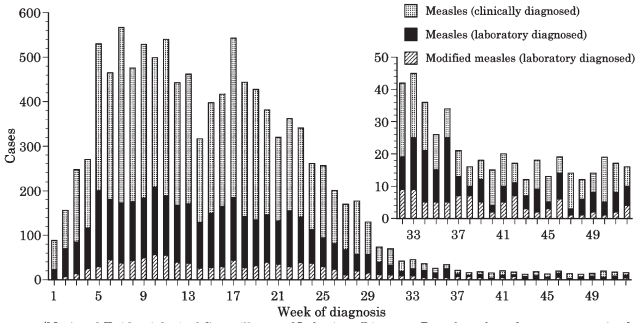
The male cases dominated the female cases in number (6,426 for male vs. 4,581 for female). In the age distribution, there were two peaks, 0-1 year and 15-16 years. More than 200 cases were reported for each age of 0-1 year and 8-27 years (Fig. 2). 4,910 cases had no vaccination history, 2,933 had received one dose, and 131 two doses. The vaccine history of the remaining 3,033 was unknown. Most 0-year-old cases had no vaccination at all (see p. 31 of this issue).

When prefectures were compared for the incidence of measles, Kanagawa (3,558), Hokkaido (1,460), Tokyo (1,174) and Chiba (1,071) were the top four. The measles cases reported in the metropolitan area, Kanagawa, Tokyo, Chiba and Saitama (388) combined, accounted for 56% of the total. The other prefectures where more than 100 cases were reported were Fukuoka, Osaka, Shizuoka, Aichi, Kyoto, Akita, Hyogo, Hiroshima, and Okayama (Fig. 3).

As for complications, nine measles encephalitis cases (all were ≥10 years) were reported in 2008 (the same number as in 2007).

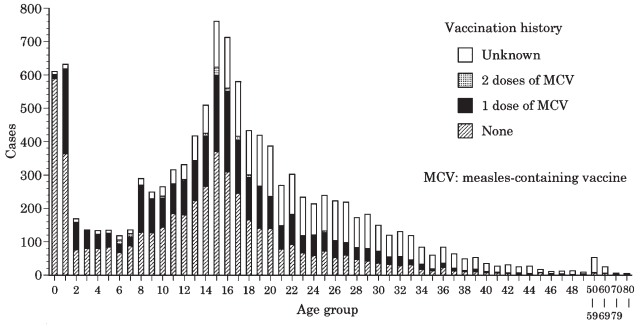
School outbreaks: From April 6 to July 19 in 2008, there were 64 temporary closures of a school, 45 temporary closures of the same year classes, and 14 temporary closures of a class or classes, amounting to 123 partial or total closures of schools reported to the Ministry of Health Labour and

Figure 1. Weekly measles cases from week 1 to week 52 of 2008, Japan



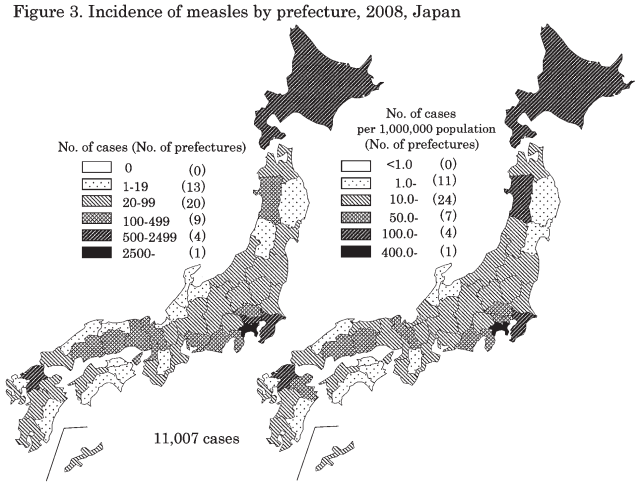
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before January 21, 2009)

Figure 2. Age distribution of measles cases by vaccination history, 2008, Japan



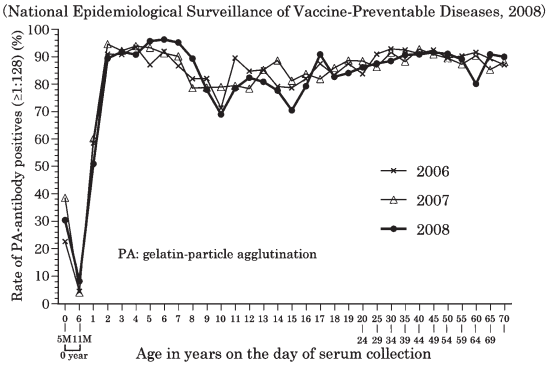
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before January 21, 2009)

Figure 3. Incidence of measles by prefecture, 2008, Japan



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before January 21, 2009)

Figure 4. Measles antibody prevalence by age, 2006-2008, Japan
(National Epidemiological Surveillance of Vaccine-Preventable Diseases, 2008)



Welfare (MHLW). The number was about one third of that in the same period of 2007 (363). The highest number of the closures was in high schools (59), followed by junior high schools (27), primary schools (14) and universities/colleges (11) (http://idsc.nih.go.jp/idwr/kanja/measreport/meas08/meas08-15.pdf).

Situations of epidemics in different prefectures in 2008: In the prefectures which experienced larger number of measles cases in 2008, measles epidemics had already started in 2007 (IASR 29: 128-129, 2008). Akita Prefecture experienced a sudden surge of measles in week 51, and the local government temporarily suspended unimmunized children from school to prevent further spread of the infection (IASR 29: 102-103, 2008). Chiba Prefecture experienced two outbreaks, the first one in primary and junior high schools in weeks 5-12 and the second one in high schools and in the local communities in weeks 21-29; the latter was triggered by students' participation in the High School Judo Championship (see p. 32 of this issue). Okinawa Prefecture experienced two outbreaks caused by measles brought into the island from outside in occasions of a live concert in March and an outdoor barbecue in August (see p. 34 of this issue).

Isolation and detection of measles virus: Measles virus has 8 clades from A to H, and 23 genotypes. In Japan, the epidemic of 2001 was caused by D5. In 2002-2003, H1 became predominant (IASR 25: 60-61, 2004). Since 2006, D5 has been circulating (http://idsc.nih.go.jp/iasr/measles-e.html). From January to December of 2008, 27 prefectural and municipal public health institutes (PHIs) in the metropolis and 21 prefectures isolated or detected 264 measles viruses (as of January 22, 2009). Among 188 strains genotyped, 175 were D5. The remaining 13 consisted of 5 strains of H1 obtained from 3 and 2 domestic cases in Osaka in March (IASR 29: 160-161, 2008) and Chiba in May, respectively, one strain of D4 from a case in Osaka in May who came back from Israel and developed symptoms 3 days later (see p. 39 of this issue), and 7 strains of A (vaccine type) from vaccinees within 3 weeks after vaccination.

The National Epidemiological Surveillance of Vaccine-Preventable Diseases: Antibody positives are defined as those having measles antibody titer higher than 1:16 in the gelatin particle agglutination assay (PA). However, it is considered that antibody titer ≥1:128 is necessary for protection from measles (see p. 40 of this issue). In 2008, only 51% of one-year-old children were antibody positive (≥1:128) (Fig. 4). Among 5-7-years children, antibody positive rate exceeded 95%, which was high reflecting the second vaccination that started in 2006. The antibody positive rate increased in 12-year-old and 17-year-old age groups, reflecting the second vaccination temporarily introduced in 2008. Generally, however, among 10s, especially at 10 and 15 years the antibody positive rate was low, and, even among age groups above twenty, there were many people possessing antibody titer below 1:128.

Vaccination rate: The second vaccination rate (% of the target age population) in the first half of 2008 fiscal year in Japan was 51% for 5-6 years, 56% for 12-13 years and 48% for 17-18 years (as of the end of September) (see p. 43 of this issue). Among prefectures, Fukui was the highest in the vaccination rate, 67%, 84% and 73% for the three respective target ages. The prefectures with the lowest coverage for three target cohorts were Miyazaki (40%), Osaka (44%) and Tokyo (32%), respectively (http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou21/index.html). Fukui Prefecture has established a system to identify unvaccinated persons, and has advised the unvaccinated persons individually to receive vaccination (IASR, 29: 191-193, 2008). In Hamamatsu City, the high second vaccination rates for 12-13 years (75%) and 17-18 years (72%) were attained by promoting vaccination in cooperation with the school nurses in junior high and high schools (see p. 44 of this issue).

Further measures needed in future: For attaining measles elimination, further increase of the vaccine coverage is necessary. For eliminating measles in 0-year infants, there is no other means than total elimination of measles from Japan (see p. 31 of this issue). For the people of the three target cohorts, the second vaccination is to be covered by public expense till the end of March in this year, but thereafter from April 1 it has to be covered by private expense. Therefore, unvaccinated persons are advised to receive vaccination before the end of this fiscal year. During the Children's Immunization Week from February 28 (Saturday) to March 8 (Sunday), in some areas, doctors will open the consultation room in holidays or in evenings for vaccination.

The Special Infectious Disease Prevention Guidelines on Measles (MHLW, December 28, 2007) requests laboratory diagnosis for all the measles cases once the measles case number is reduced to a certain level. In June 2008, PHIs and National Institute of Infectious Diseases agreed to establish the Measles-Rubella Reference Centers as a collaborative mechanism and revised the Measles Laboratory Diagnosis Manual to enforce the laboratory diagnosis practice (see p. 45 of this issue). On January 15, 2009, MHLW sent a correspondence "Strengthening the Framework of Measles Laboratory Diagnosis" to the local governments (see p. 47 of this issue). Definitive diagnosis assisted by the laboratory diagnosis is indispensable for preventing the spread of measles in the community, particularly when we encounter the possible first case whose contact source is unclear.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Enteric Infection in Japan, have provided the above data.

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<THE TOPIC OF THIS MONTH>
Tetanus in Japan as of December 2008

Clostridium tetani is an obligate anaerobic gram-positive bacillus forming a terminal spore. While *C. tetani* in the vegetative form is sensitive to heat and oxygen, its spore is resistant to heat, oxygen and most antiseptics. The spores are found widely in soil or in the animals' intestines and feces. The spores, once entering the body tissues through a wound, germinate and grow under anaerobic conditions producing tetanus toxin (see p. 68 of this issue). The toxin is circulated in the blood stream and reaches central nervous system, such as ventral horn or brain stem. Once the toxin is fixed to the endplate of motor neuron, inhibitory neural circuit is blocked. The consequence is the typical manifestation of tetanus infection. The incubation period for tetanus is usually 3-21 days. However, longer incubation period exceeding one month has been reported. Characteristic symptoms are contraction of the muscle at the injury site, trismus, risus sardonicus (a rigid smile), dysphagia, dyspnea, and opisthotonus. If the treatment is delayed, case-fatality rate is high.

Depending upon the cause and patient profile, tetanus is categorized into two following forms.

1. Wound tetanus: It is most common in adults. Infection usually occurs through deep puncture wounds or cuts or even through tiny breaks of skin such as pinprick or scratch (IASR 28: 47-49, 2007). *C. tetani* infections through pyorrheal legions or through self-administration of insulin or self-sampling of blood among diabetic patients have been reported. In the United States and in the United Kingdom, tetanus cases among injection-drug abusers have been reported, indicating possible infection through spore-contaminated drugs, solutions, needles or syringes (see p. 70 of this issue).

2. Neonatal tetanus: Tetanus infection occurs in newborns at the time of delivery and during the postnatal period in unhygienic circumstances. After 1-2 weeks of incubation, early symptoms appear, for example, baby's sucking power weakens. Once tetanus symptoms become manifest, 60-90% of newborns will die within 10 days. In developing countries, tetanus is a major cause of neonatal deaths. According to the WHO's estimate, neonatal tetanus killed about 128,000 babies in the world in 2004 (see p. 70 of this issue). In Japan, a neonatal tetanus case occurred in 2006 after an 11-year absence (IASR 29: 50-51, 2008).

Incidence of tetanus: Tetanus is classified as a category V notifiable infectious disease under the Infectious Diseases Control Law and physicians must notify the case to the nearby health center within 7 days after diagnosis (for reporting guidelines, refer to http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-12.html).

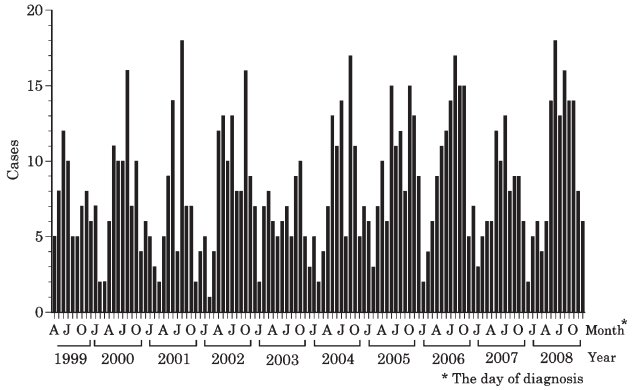
Since the enactment of the Infectious Diseases Control Law, the number of reported cases, which is about 100 cases per year, remained unchanged (Table 1 and additional data on p. 67 of this issue). Tetanus cases tend to increase from May to October when the outdoor activities are high (Fig. 1). Of 546 cases reported during 2004-2008, 513 patients (94%) were older than forty, and the proportion of those in their 60s-70s became higher than in 1999-2003 (Fig. 2). The male cases dominated the female cases in number,

Table 1. Cases and deaths of tetanus in Japan, 1999-2008

Year	Cases*	Deaths**
1999	66	10
2000	91	10
2001	80	12
2002	106	9
2003	73	7
2004	101	9
2005	115	7
2006	117	5
2007	89	7
2008	124	7

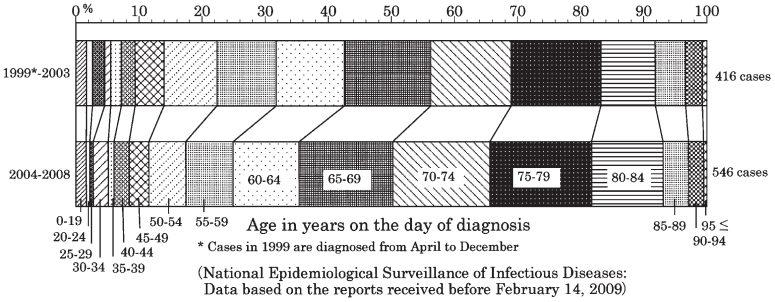
*Cases by year of diagnosis. Cases in 1999 were diagnosed from April to December.
(National Epidemiological Surveillance of Infectious Disease: Data based on the reports received before February 14, 2009)
**Deaths in 2008 are provisional data from January to September.
(Vital Statistics in Japan, Ministry of Health, Labour and Welfare)

Figure 1. Monthly incidence of tetanus in Japan, April 1999-December 2008



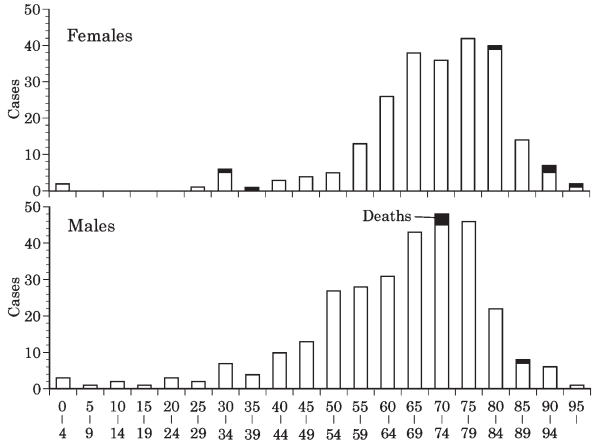
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before February 14, 2009)

Figure 2. Age distribution of tetanus cases in Japan, 1999-2003 vs. 2004-2008



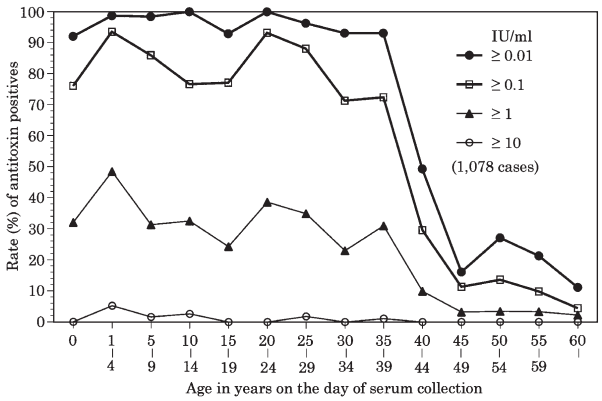
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before February 14, 2009)

Figure 3. Age distribution of tetanus cases, by gender, 2004-2008, Japan



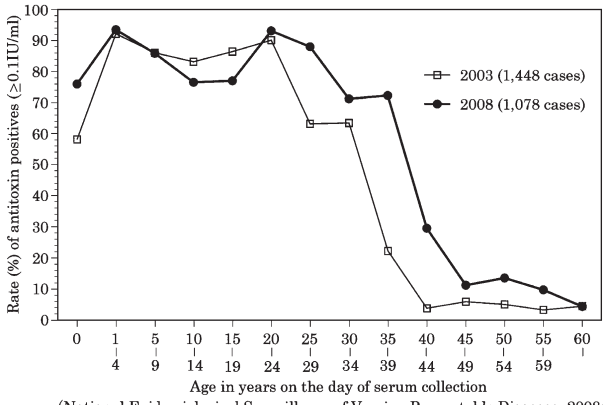
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before February 14, 2009)

Figure 4. Tetanus antitoxin prevalence by age, 2008, Japan



(National Epidemiological Surveillance of Vaccine-Preventable Diseases, 2008: Data based on the reports received before February 19, 2009)

Figure 5. Tetanus antitoxin prevalence by age, 2003 vs. 2008, Japan



(National Epidemiological Surveillance of Vaccine-Preventable Diseases, 2008: Data based on the reports received before February 19, 2009)

but among patients older than 80-year-old individuals, there were more females than males (Fig. 3). Tetanus cases were reported in all prefectures. According to the Vital Statistics in Japan (Table 1), there were 35 deaths in 2004-2008, meanwhile, during the same period, number of fatal cases reported at the time of notification or additionally later was only ten, far less than the figures appearing in the Vital Statistics. When the notified cases died or when laboratory diagnosis was obtained after the notification, such information should be sent to the health center in compliance with the National Epidemiological Surveillance of Infectious Diseases (NESID).

Age-specific tetanus antitoxin prevalence: According to the provisional report of the National Epidemiological Surveillance of Vaccine-Preventable Diseases in 2008 (1,078 samples from healthy individuals, as of February 19, 2009), the rate of antitoxin positives (those with antitoxin titer higher than 0.01 IU/ml which is the minimum level of protective immunity to tetanus) was 92% among 0-year-old infants, 99% among 1-4 year-olds, and as high as ≥92% among individuals up to 35-39 years (Fig. 4). Among the 45-49 to 55-59 year-old individuals, the positive rate was 25%, and for those older than 60 years it was as low as 11%. By comparing the present survey data in 2008 with the previous one in 2003 (the first anti-tetanus serosurvey of adult population in Japan), it was found that the age groups with high incidence of high antitoxin titers (U ≥ 0.1 IU/ml giving a sufficiently high level of protective immunity) expanded to older ages by five years (Fig. 5). It indicates that the immunity was maintained for five years even among adult populations. This could be confirmed further by the next survey planned for 2013.

Diagnosis and treatment: The diagnosis is usually made clinically by the characteristic symptoms of tetanus, i.e., unopposed muscle contraction and spasm. Isolation of *C. tetani* from infection site and detection of tetanus toxin produced by the isolates will confirm the diagnosis (see p. 69 of this issue). If tetanus was suspected from symptoms, the treatment, through debridement of wounds and administration of anti-tetanus human immune globulin (TIG) should begin without delay. Antibiotics are used when necessary. To treat spasms, anticonvulsants are used. Suspected tetanus cases should be transported to the hospital equipped with emergency intensive care unit in early stage since many cases need respiratory control (the Japan Medical Association, Diagnosis and Treatment Guidelines for Infectious Diseases, 2004).

For injuries that may be associated with tetanus infection, TIG and tetanus toxoid vaccine (T) should be administered in addition to cleaning and disinfection of the wound. If primary immunization has been completed, even when one encounters unexpected traffic accident, injection of T may boost antibody titer and prevent clinical manifestation of tetanus.

Immunization to adults: The case-fatality rate of tetanus was 81% in 1950; the notified cases of tetanus totaled up to 1,915, of which 1,558 died and the greater part of the death cases were aged under 15 years (IASR 23: 1-2, 2002). Cases and deaths of tetanus decreased in number after introduction of T in 1953 (voluntary immunization) and the start of routine immunization of diphtheria-tetanus-pertussis combined vaccine (DTP) in 1968 accelerated the decrease. Majority of recent tetanus cases were born before the introduction of DTP routine immunization, ≥40 years, and their tetanus antibody positive rate is low, meanwhile among those born after the start of DTP routine immunization, <40 years, tetanus antibody positive rate is high and tetanus cases are fewer. It could be stated that the immunity against tetanus obtained through vaccination is effective enough to prevent clinical manifestation of tetanus. To reduce tetanus cases, it is necessary to immunize the generation aged ≥40 years. Those who have no vaccination history of DTP, DT or T should receive two doses of T within a year first and then another in the next year to obtain the basic immunization status (see p. 71 of this issue).

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Enteric Infection in Japan, have provided the above data.

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Control Division,
Ministry of Health, Labour and Welfare

<THE TOPIC OF THIS MONTH>
Typhoid fever and paratyphoid fever in Japan, 2005-2008

Typhoid fever and paratyphoid fever are caused respectively by *Salmonella enterica* subsp. *enterica* serovar Typhi (*S.* Typhi) and *Salmonella enterica* subsp. *enterica* serovar Paratyphi A (*S.* Paratyphi A). They are characterized by ulceration of Peyer's patches in the ileum and multiplication of the bacteria in the reticuloendotherial system followed by bacteremia. The clinical picture is distinct from nontyphoidal *Salmonella* infections. *S.* Sendai, *S.* Paratyphi B, and *S.* Paratyphi C cause symptoms similar to typhoid fever but they are treated as nontyphoidal *Salmonella* infections in Japan.

Typhoid fever and paratyphoid fever were categorized as category II infectious diseases in the Infectious Diseases Control Law enacted in April 1999 (IASR 22: 55-56, 2001 & 26: 87-88, 2005), but are now categorized as category III infectious diseases after enactment of the revised version of the law in April 2007. Physicians are under obligation of notifying the prefectural governor through the nearest health center when they have made confirmed diagnosis of patients or asymptomatic carriers or when they encountered confirmed or suspected deceased cases (http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01.html). Prefectural health departments are under obligation of sending isolates from the patients or carriers to National Institute of Infectious Diseases (NIID). The Department of Bacteriology, NIID performs phage typing and drug-sensitivity testing and provides results back to the prefectures, which also appear on the IASR web site (http://idsc.nih.go.jp/iasr/virus/bacteria-e.html).

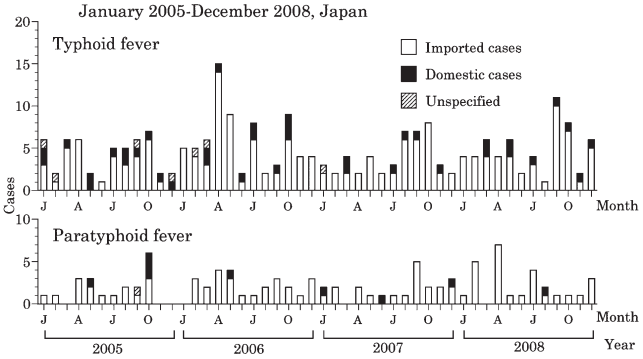
National Epidemiological Surveillance of Infectious Diseases (NESID): Reported cases (including patients and carriers, hereafter) of typhoid fever was 50 in 2005, 72 in 2006, 47 in 2007, and 58 in 2008 (Table 1). The number of paratyphoid fever reported in 2005-2008 remained in the range of 20-27 per year. Many of the typhoid and paratyphoid cases were imported

Table 1. Incidence of typhoid and paratyphoid fever in Japan, 2005-2008

Year	Typhoid fever			Paratyphoid fever		
	Cases*	%	Isolates**	Cases*	%	Isolates**
2005	50 (34)	68%	31 (21)	20 (15)	75%	12 (12)
2006	72 (60)	83%	60 (46)	26 (25)	96%	19 (17)
2007	47 (40)	85%	37 (26)	22 (19)	86%	19 (15)
2008	58 (49)	84%	45 (35)	27 (26)	96%	20 (19)

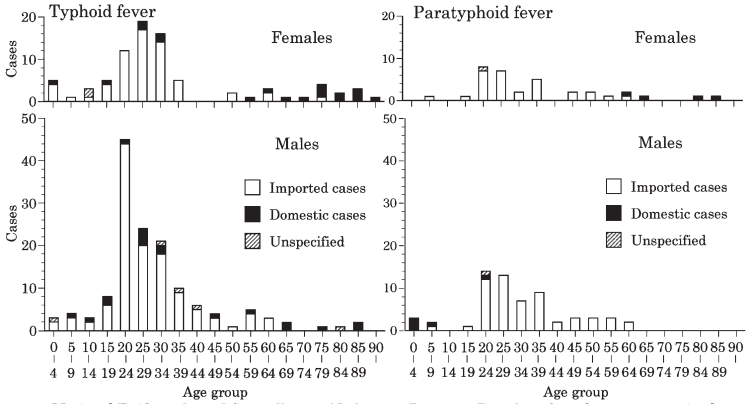
*Confirmed and suspected patients and carriers, ( ): Imported cases included in the total, %: Ratio of imported cases to the total
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before March 12, 2009)
**Strains forwarded to the Department of Bacteriology, the National Institute of Infectious Diseases.

Figure 1. Monthly incidence of typhoid and paratyphoid fever, January 2005-December 2008, Japan



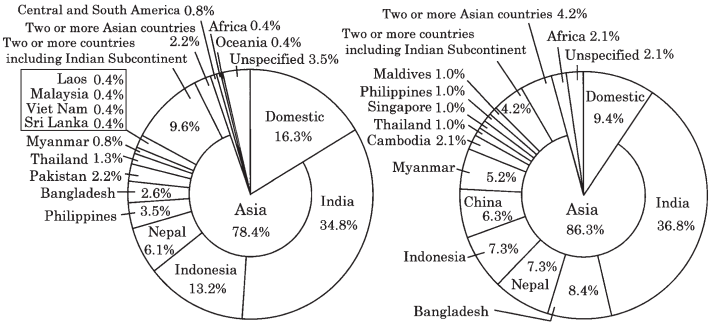
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before March 12, 2009)

Figure 2. Age distribution of typhoid and paratyphoid fever cases, 2005-2008, Japan



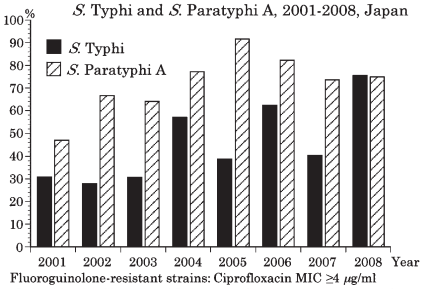
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before March 12, 2009)

Figure 3. Typhoid and paratyphoid fever cases in Japan, by suspected region of infection, 2005-2008



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before March 12, 2009)

Figure 4. Ratios of isolates with decreased susceptibility or resistant to fluoroquinolones to total isolates of *S.* Typhi and *S.* Paratyphi A, 2001-2008, Japan



Fluoroguinolone-resistant strains: Ciprofloxacin MIC ≥4 μg/ml
(Judged by the Clinical and Laboratory Standards Institute breakpoint)
Low-level fluoroguinolone-resistant strains:
Ciprofloxacin MIC ≥0.125 to <4 μg/ml
(Data from the Department of Bacteriology, the National Institute of Infectious Diseases)

ones, occupying 81% of typhoid fever cases and 93% of paratyphoid cases. Cases occurred more frequently in April-May and September-October seasons (Fig. 1). Males are affected more frequently than females, and 20-39 year-old individuals occupy 67% of all the patients (Fig. 2). The clustering of the age of the cases to 20-39 years is probably because young students or office workers traveled abroad during spring and summer vacations to South-East Asia, Indian subcontinent and other endemic area of this disease. The time lag of about two months between infection (travel in these countries during vacation seasons) and diagnosis (the peak seasons of the report of this disease) is probably caused by the time elapsed from infection to the final diagnosis.

Among countries where the typhoid and paratyphoid cases were presumed to have acquired infection in 2005-2008 (Fig. 3), 78% were Asian countries for typhoid cases, such as India (79 cases), Indonesia (30 cases), Nepal (14 cases), Philippines (8 cases), Bangladesh (6 cases), Pakistan (5 cases), Thailand (3 cases), Myanmar (2 cases), and Sri Lanka, Viet Nam, Malaysia, and Laos (1 case each). Twenty-seven cases had journeyed in Indian subcontinent passing through more than two countries. Countries visited by the cases other than Asian countries were Central South America (2 cases), Africa, and Oceania (1 case each). For paratyphoid cases, Asia occupied 86%, such as, India (35 cases), Bangladesh (8 cases), Nepal (7 cases), Indonesia (7 cases), China (6 cases), Myanmar (5 cases), Cambodia (2 cases), Thailand, Singapore, Philippines, and Maldives (1 case each). Eight cases visited two or more Asian countries, and two visited African countries.

Phage types: The most frequent phage type for *S.* Typhi in 2005-2008 was E1 (Table 2). Among isolates from cases infected in India, most frequent was also phage type E1, but E9 that increased in 2004 was also isolated in 2006-2008. Phage type M1 was isolated in low numbers, 2-5, in every year. For *S.* Paratyphi A (Table 3), though predominant were phage types 2, 4 and 6 in 2005, phage type 1 became predominant in 2006 and persisted later together with phage types 2, 4 and 6.

Drug-resistance and therapy: Typhoid and paratyphoid fever are treated with oral administration of fluoroquinolones. In recent years, however, *S.* Typhi and *S.* Paratyphi A lowly sensitive to fluoroquinolones have been isolated at high frequencies (Fig. 4). *S.* Typhi strains resistant to fluoroquinolones were isolated from three patients (2 in 2006 and 1 in 2007) who traveled in India (see p. 93 of this issue). As fluoroquinolones are ineffective to such patients, high body temperature persists and recovery needs long treatment. For such cases, the third generation cephem antibiotics and macrolides are used in combination (see p. 93 of this issue).

Table 2. Phage types of *S.* Typhi isolates in Japan, 2005-2008

Phage type	2005	2006	2007	2008
A	1	5 (4)	4 (1)	–
B1	5 (4)	7 (4)	1 (1)	1
C4	1	–	–	–
D1	2 (1)	1	–	–
D2	2 (1)	2 (1)	1 (1)	1
E1	6 (6)	18 (16)	10 (7)	21 (19)
E14	–	–	1 (1)	–
E2	1 (1)	–	–	–
E9	–	6 (6)	3 (3)	9 (7)
J1	1 (1)	–	–	–
M1	2	3	5 (2)	4 (2)
O	–	–	–	1 (1)
35	–	3 (3)	–	–
40	–	1	–	–
46	1 (1)	–	–	–
61	–	–	1	–
DVS	4 (3)	3 (2)	3 (2)	–
UVS1	1 (1)	–	2 (2)	2 (1)
UVS2	–	3 (3)	3 (3)	4 (3)
UVS3	–	–	1 (1)	1 (1)
UVS4	4 (2)	8 (7)	2 (2)	1 (1)
Total	31 (21)	60 (46)	37 (26)	45 (35)

DVS: Degraded Vi-positive strain
UVS1: Untypable Vi-positive strain group 1
UVS2: Untypable Vi-positive strain group 2
UVS3: Untypable Vi-positive strain group 3
UVS4: Untypable Vi-positive strain group 4
( ): Imported cases included in the total
(Data from the Department of Bacteriology, the National Institute of Infectious Diseases)

Table 3. Phage types of *S.* Paratyphi A isolates in Japan, 2005-2008

Phage type	2005	2006	2007	2008
1	1 (1)	6 (5)	8 (5)	8 (8)
2	4 (4)	3 (3)	3 (3)	3 (3)
3	–	–	1	–
4	3 (3)	1 (1)	2 (2)	1 (1)
5	–	–	–	1 (1)
6	3 (3)	5 (4)	2 (2)	1 (1)
UT	1 (1)	4 (4)	3 (3)	6 (5)
Total	12 (12)	19 (17)	19 (15)	20 (19)

UT: untypable, ( ): Imported cases included in the total
(Data from the Department of Bacteriology, the National Institute of Infectious Diseases)

Summary: In endemic areas, infection primarily occurs via consumption of contaminated water or foods. Consumption of unboiled water, raw fruits and uncooked food materials should be avoided while traveling in such areas. Those who plan a trip to Indian subcontinent where fluoroquinolone low sensitive or resistant strains were isolated may have to consider vaccination as one of preventive measures (see p. 95 & 96 of this issue).

As it is becoming increasingly important to monitor drug resistant strains that may compromise the therapy, it is requested that increasing efforts are made for isolating bacteria from typhoid and paratyphoid fever patients and sending them to NIID (Notice from the Ministry of Health, Labour and Welfare, IASR 29: 314-315, 2008).

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Enteric Infection in Japan, have provided the above data.

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<THE TOPIC OF THIS MONTH>
Enterohemorrhagic *Escherichia coli* infection in Japan as of April 2009

Enterohemorrhagic *Escherichia coli* (EHEC) infection is among the category III notifiable infectious diseases in the National Epidemiological Surveillance of Infectious Diseases (NESID) under the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (Infectious Diseases Control Law) enforced in April 1999. It requires mandatory notification from the physicians immediately after diagnosis through isolation of EHEC and confirmation of Verocytotoxin (VT). Since April 2006 when the case definition was amended, notification is needed for hemolytic uremic syndrome (HUS) if VT is positive in stool specimens, or anti-O-antigen agglutinating antibody or anti-VT antibody is positive in serum even when bacterial isolation has not been done (http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-03-03.html). When the physicians have notified the EHEC infection as food poisoning, or when the director of the health center has recognized some cases as food poisoning, the prefectural government conducts investigation and reports the results to the Ministry of Health, Labour and Welfare in compliance with the Food Sanitation Law.

EHEC infection is a target disease of pathogen surveillance under the NESID. Prefectural and municipal public health institutes (PHIs) conduct isolation of EHEC, serotyping, and VT typing, and the Department of Bacteriology, National Institute of Infectious Diseases (NIID), conducts molecular epidemiological analysis of the isolates and provides the data through the PulseNet Japan (see p. 124 of this issue).

Cases notified under NESID: In 2008, EHEC infections, including both symptomatic patients and asymptomatic carriers were 4,330, exceeding 4,000 for the second consecutive year (Table 1 and IASR 29: 117-118, 2008). There is a regular seasonal variation with a large peak in summer seasons (see the weekly incidence in Fig. 1). In 2008, incidence per 100,000 population was highest in Saga Prefecture (19.97) followed by Iwate (11.91), Fukui (9.49) and Nagasaki (9.40). There was wide regional variation in the incidence of EHEC infection (Fig. 2, left). The prefectures with higher incidence in 2005-2007 tended to report higher incidence of EHEC infection in 2008 too. As in preceding years, incidence of EHEC infection was highest among the age group of 0-4 years followed by 5-9 year age group (Fig. 3). When the incidence among 0-4 year age group was compared for different prefectures, highest incidence was reported from Saga and Iwate Prefectures, which experienced EHEC outbreaks in nursery schools and kindergartens (Fig. 2, right). Among EHEC infected population younger than 14 years, there were more males than females, while among the population older than 15 years there were more females than males. Percentage of symptomatic patients among the infected was high for young (≤14 years) and advanced ages (≥70 years), 73% for the both, and relatively low, less than 43%, for those in their thirties and forties (Fig. 3). Eight deceased cases of HUS or acute renal failure were reported in 2008.

Isolation of EHEC: In 2008, PHIs reported to the Infectious Disease Surveillance Center (IDSC), NIID 2,471 isolations, which number was about half of the number of reported EHEC infection cases, 4,330 (Table 1). The discrepancy is due to the present situation where a substantial amount of the laboratory data obtained outside of PHIs does not reach NIID. O157 that increased to 75% in 2007 decreased to 65% in 2008. O26 increased from 13% in 2007 to 24% in 2008. O111 that was 6% in 2007 slightly decreased to 4% in 2008 (http://idsc.nih.go.jp/iasr/virus/bacteria-e.html). Varieties of other serotypes have been obtained in addition.

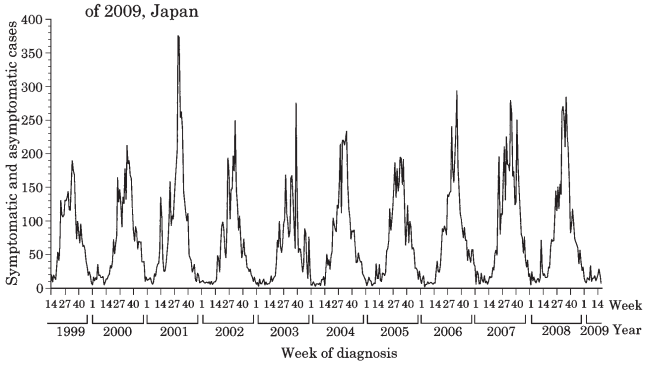
As there are strains that cannot be identified serotype by the commercially available anti-sera (IASR 25: 141-143, 2004), confirmation of EHEC by detection of VT is indispensable for its identification. In 2008, VT1&2 occupied 61% of O157 (53-68% in 1997-2007), VT1 alone 96% of O26, and VT1 alone 36% of O111 (less than in preceding years).

Table 1. Notified cases of EHEC infection

Year	Period	Cases	
1996	Aug. 6-Dec. 31	1,287	*
1997	Jan. 1-Dec. 31	1,941	*
1998	Jan. 1-Dec. 31	2,077	*
1999	Jan. 1-Mar. 31	108	*
1999	Apr. 1-Dec. 31	3,115	**
2000	Jan. 1-Dec. 31	3,652	**
2001	Jan. 1-Dec. 31	4,436	**
2002	Jan. 1-Dec. 31	3,186	**
2003	Jan. 1-Dec. 31	2,998	**
2004	Jan. 1-Dec. 31	3,760	**
2005	Jan. 1-Dec. 31	3,594	**
2006	Jan. 1-Dec. 31	3,922	**
2007	Jan. 1-Dec. 31	4,617	**
2008	Jan. 1-Dec. 31	4,330	**
2009	Jan. 1-Apr. 14	247	**

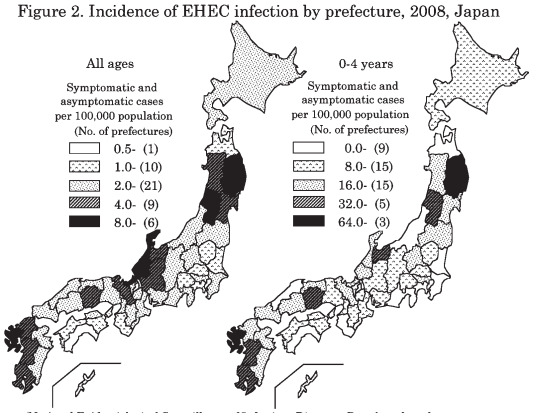
Including symptomatic and asymptomatic cases
*Statistics on Communicable Diseases in Japan (Ministry of Health and Welfare)
**National Epidemiological Surveillance of Infectious Diseases
(Data based on the reports as of April 14, 2009)

Figure 1. Weekly incidence of EHEC infection from week14 of 1999 to week15 of 2009, Japan



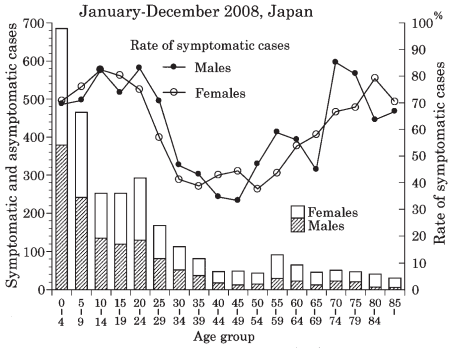
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before April 14, 2009)

Figure 2. Incidence of EHEC infection by prefecture, 2008, Japan



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before April 14, 2009)

Figure 3. Age distribution of cases of EHEC infection, January-December 2008, Japan



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before April 14, 2009)

Among 2,471 cases in 2008 from which EHEC was isolated, 1,611 cases were O157 infections. Of 1,541 data-available O157 cases, the main symptoms were diarrhea (57%), abdominal pain (53%), bloody diarrhea (39%) and fever (21%) (see p. 121 of this issue). There were 26 HUS cases (8 cases of VT2 and 18 cases of VT1&2). One HUS case (VT2) was found among 34 O145 cases. The incidence of HUS cases was 1.9% of all the symptomatic cases and was less than that in NESID, 3.3% (see p. 122 of this issue). It is because, as indicated above, in NESID, the reported HUS cases include those positive only for VT in stool specimens or for anti-O-antigen agglutinating antibody or anti-VT antibody in serum (without bacterial isolation). The percentage of asymptomatic carriers was 52% in O26 cases (see p. 121 of this issue).

Outbreaks: In 2008, PHIs reported 37 EHEC outbreaks to IDSC, 21 incidents of which were caused by O157. There were 20 outbreaks each involving 10 or more EHEC-positive cases (Table 2). Among them, 4 incidents were suspected to be foodborne, and 12 incidents person-to-person infections. In 2008, 17 EHEC incidents involving 115 patients were reported by prefectures in compliance with the Food Sanitation Law (25 incidents and 928 patients in 2007). The number of EHEC patients reported in compliance with the Food Sanitation Law is far lower than that reported according to the Infectious Diseases Control Law. This is because many cases lacked direct evidence of implication of food(s) as the causative material, and also because in reality EHEC infections involving only one person are rarely reported as food poisoning.

In 2008, there were 13 outbreaks in nursery schools and kindergartens, which was almost as frequent as in previous years. As small numbers of bacteria are sufficient for establishing infections, EHEC can easily spread from person to person. For preventing outbreaks in nursery schools or kindergartens, proper sanitation measures, such as routine hand washing by children and staff and keeping padding pools for children in sanitary condition during summer, are necessary. Spread of infection within a family is not infrequent. Once a patient has appeared in a family, the health center should provide the family with thorough instructions necessary for preventing the secondary infections.

Foods contaminated with small number of EHEC can cause foodborne infection. Therefore, it is important to keep basic practice for preventing food poisoning. It is also important to avoid feeding those with weak immunity including younger children and the elderly with raw or undercooked meat (http://www.mhlw.go.jp/topics/syokuchu/03.html).

Update 2009: During weeks 1-15 of this year, 247 EHEC cases were reported (Table 1). EHEC O121 was isolated from 31 cases in an outbreak at a nursery school in Oita Prefecture during weeks 5-6. As EHEC infection increases in every summer, increased vigilance on this infection is requested from now.

Table 2. Outbreaks of EHEC infection, 2008

No.	Prefecture /City	Period	Suspected route of infection	Setting of outbreak	Serotype	VT type	Symptomatic cases	Consumers	Positives /examined	Familial infection	Reference in IASR
1	Saga P.	Mar. 7-24	Foodborne	High school*	O26:H11	VT1	91	249	75 / 477	Yes	Vol. 29, No. 6
2	Oita P.	Mar. 12-24	Person to person	Nursery school	O157:H-	VT1&2	3	···	10 / 102	Yes	p. 125 of this issue
3	Kyoto C.	May 24-Jun. 14	Person to person	Nursery school	O26:H11	VT1	N.D.	···	27 / 207	Yes	
4	Nagasaki C.	Jun. 9-21	Unknown	Hospital	O111:H-	VT1&2	67	···	32 / 217	Yes	Vol. 30, No. 3
5	Kanagawa P.	Jun. 11-13	Unknown	High school**	O26:H11	VT1	52	···	25 / 36	No	Vol. 29, No. 9
6	Toyama P.	Jun. 20-Jul. 6	Person to person	Nursery school	O26:H11	VT1	8	···	34 / ?	Yes	p. 126 of this issue
7	Yamagata P.	Jun. 20-Jul. 13	Unknown	Not specified	O111:H-	VT1	6	···	13 / 116	Yes	
8	Fukui P.	Jul. 7-23	Foodborne	Restaurant (meat)	O157:H7	VT1&2	6	23	11 / 41	No	Vol. 29, No. 12
9	Osaka P.	Jul. 19-	Person to person	Nursery school	O157:H7	VT2	17	···	18 / 112	Yes	Vol. 30, No. 3
10	Tokyo M.	Jul. 29-Aug. 27	Person to person	Nursery school	O26:H-	VT1	18	···	32 / 308	Yes	p. 127 of this issue
11	Tokyo M.	Aug. 2-Sep. 26	Person to person	Nursery school	O26:H-	VT1	2	···	14 / 207	Yes	p. 127 of this issue
12	Fukui P.	Aug. 25-31	Foodborne	Other place (meat)	O157:H7	VT1&2	10	53	12 / 51	No	Vol. 30, No. 1
13	Iwate P.	Aug. 27-Sep. 28	Unknown	Two kindergartens	O26:H11	VT1	29	···	84 / 475	Yes	p. 128 of this issue
14	Yamagata P.	Aug. 30-Oct. 28	Person to person	Home, nursery school & kindergarten	O145:H-	VT1	6	···	13 / 176	Yes	p. 130 of this issue
15	Fukuoka C.	Oct. 7-10	Foodborne	Other place (meat)	O157:H7	VT1&2	5	46	19 / 46	No	p. 132 of this issue
16	Tokyo M.	Oct. 11-	Person to person	Nursery school	O111:H-	VT1&2	61	···	39 / 249	?	
17	Saga P.	Oct. 14-Nov. 20	Person to person	Nursery school	O26:H11	VT1	6	···	10 / 51	Yes	p. 133 of this issue
18	Saga P.	Oct. 31-Dec. 3	Person to person	Nursery school	O157:H-	VT1&2	15	···	23 / 352	Yes	p. 133 of this issue
19	Yamagata P.	Nov. 9-	Person to person	Nursery school & kindergarten	O26:H11	VT1	N.D.	···	11 / 129	Yes	
20	Saga P.	Nov. 20-Dec. 20	Person to person	Nursery school	O157:H7	VT2	12	···	21 / 388	Yes	p. 133 of this issue

Including 10 or more EHEC-positives, M.: Metropolitan, P.: Prefecture, C.: City, N.D.: No data, *School excursion to Australia, **School excursion to Hokkaido,
··· No information was entered because person-to-person infection was suspected.
(Data based on the outbreak reports from public health institutes received before May 7, 2009 and references in IASR)

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Enteric Infection in Japan, have provided the above data.

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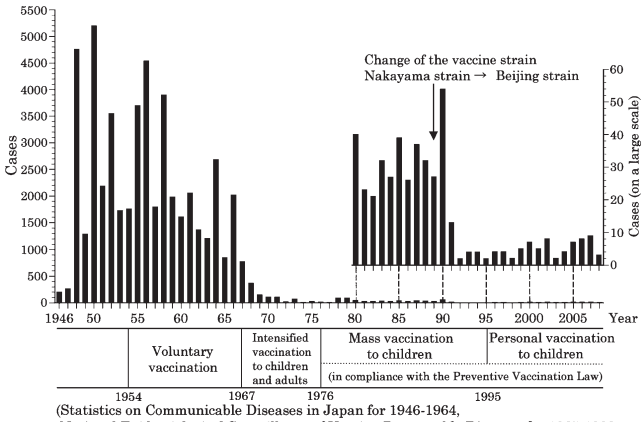
National Institute of Infectious Diseases and
Tuberculosis and Infectious Diseases
Control Division,
Ministry of Health, Labour and Welfare

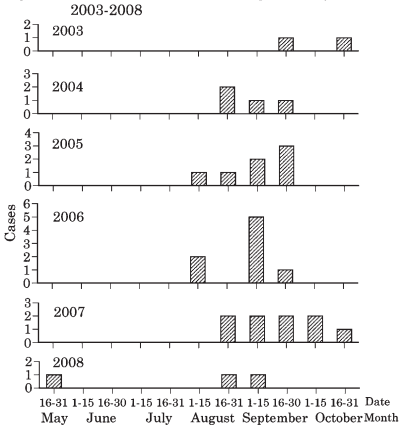
<THE TOPIC OF THIS MONTH>
Japanese encephalitis, Japan, 2003-2008

Figure 1. Incidence of Japanese encephalitis in Japan, 1946-2008



(Statistics on Communicable Diseases in Japan for 1946-1964,
National Epidemiological Surveillance of Vaccine-Preventable Diseases for 1965-1998,
National Epidemiological Surveillance of Infectious Diseases for 1999-2008)

Figure 2. Incidence of Japanese encephalitis by month, 2003-2008



(National Epidemiological Surveillance of Infectious Diseases:
Data based on the reports received before May 7, 2009)

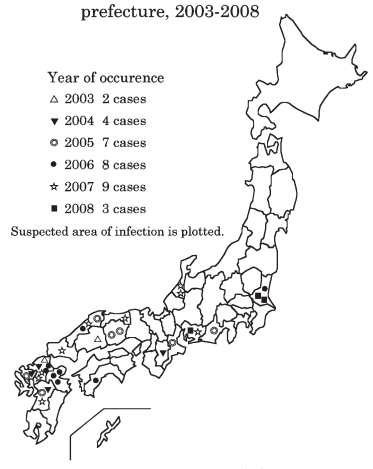
Japanese encephalitis (JE), a serious and acute form of encephalitis, is caused by JE virus (JEV) transmitted by the bite of infective mosquitoes, *Culex tritaeniorhynchus*. JE is a category IV notifiable infectious disease in the National Epidemiological Surveillance of Infectious Diseases under the Infectious Diseases Control Law enacted in April 1999. Prefectural public health institutes (PHIs) participating in the National Epidemiological Surveillance of Vaccine-Preventable Diseases have monitored herd immunity among humans and JEV infection in pigs. This article describes the trend of JE in 2003-2008 (for the data of preceding years, see IASR 24: 149-150, 2003).

Incidence of JE: A special intensive immunization program targeting at all age groups, particularly the elderly and children in 1967-1976 successfully reduced the number of JE cases to several dozen in the 1980s and even to nine or less from 1992 on (Fig. 1).

In six years between 2003 and 2008, total 33 JE cases were reported. They were mostly in September. The date of the onset of symptoms of the first patient of the year was on May 27 (2008, in Ibaraki Prefecture) and that of the latest was on October 30 (2003, in Hiroshima Prefecture) (Fig. 2). All the 33 JE cases occurred in 16 prefectures in the western part of Japan (Fig. 3); among them six cases occurred in Fukuoka Prefecture.

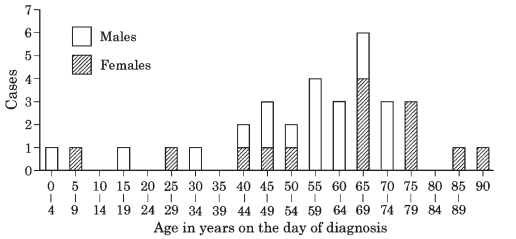
In 2005-2007 when incidence was relatively higher, among 24 cases reported, 17 cases occurred in the Kyushu and Shikoku districts. In other districts, 2 cases (1 deceased) occurred in Aichi Prefecture in 2006-2007, 2 cases in Ishikawa Prefecture in 2007 and 2 cases in Ibaraki Prefecture in 2008. The numbers of male and female cases were 19 and 14, respectively. Twenty-eight cases (85%) were aged 40 years or more, and 6 cases were 65-69 years old. There were 2 cases aged 25-34 years, and 3 cases below 20 years (Fig. 4). A 3-year-old case in 2006 had received no vaccination at all (see p. 153 of this issue).

Figure 3. Japanese encephalitis cases by prefecture, 2003-2008



(National Epidemiological Surveillance of Infectious Diseases:
Data based on the reports received before May 7, 2009)

Figure 4. Age distribution of Japanese encephalitis cases, 2003-2008



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before May 7, 2009)

There were total 4 fatal cases, which were reported at the time of notification or later as additional information. One case in 2004 was in its 20s, one case in 2006 was in its 60s, and two cases in 2007 were in its 40s and in its 80s.

Antibody prevalence among general population (see p. 149 of this issue)**:** Approximately 3,200 people in 11 prefectures were surveyed in 2008 to determine antibody prevalence (Fig. 5). Neutralizing antibody positive (antibody titer U≥10) rate in different ages revealed existence of two age groups whose antibody prevalence was low, a groups of 6 months to 5 years (<15%), and a group of 30-64 years (<50%). Comparison with the previous surveys revealed that the former group is expanding to the right, i.e., to advanced ages since 2000 and the antibody prevalence in the latter group has been decreasing since 2004. In contrast, the antibody prevalence among 9-24 years and that of ≥65 years of age remained high, 80% and ≥50%, respectively.

Figure 5. Japanese encephalitis antibody prevalence by age, 1996-2008
(National Epidemiological Surveillance of Vaccine-Preventable Diseases 2008)

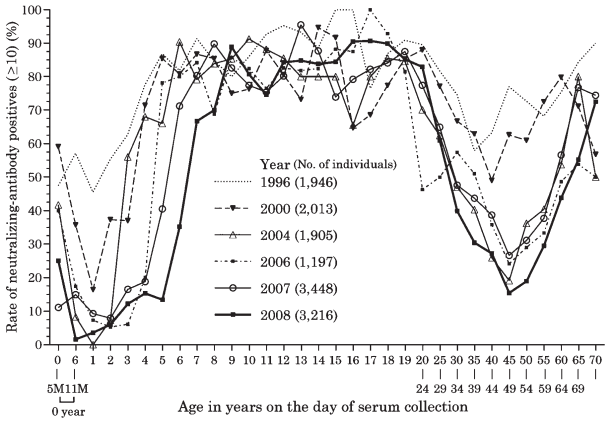
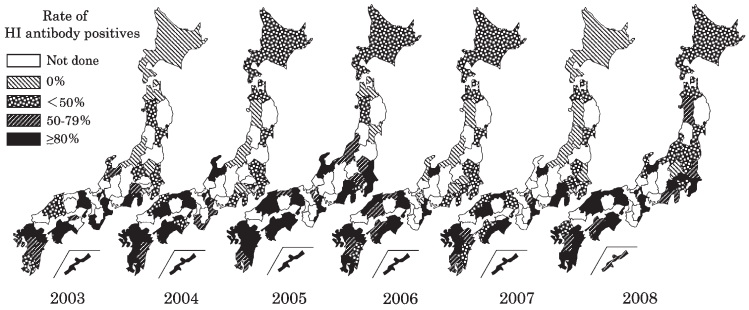


Figure 6. Japanese encephalitis virus infection in pigs, 2003-2008
(National Epidemiological Surveillance of Vaccine-Preventable Diseases)



Until the beginning of 2005, the JE vaccine was in the regular vaccination and was given in a series of three stages, the first stage consisting of 2 primary doses at 3 years of age and a booster dose at 4 years of age, the second stage a booster dose at 9-12 years of age, and the third stage a booster dose at 14-15 years of age. On May 30, 2005, however, a notice on "Withholding the use of JE vaccine in the regular vaccination (recommendation)" from the Director, Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare (MHLW) (Announcement No. 0530001) was issued and the third stage immunization was abolished on July 29, 2005. Since then, the JE vaccination rate dropped sharply, which well explains the low JE immunization status group of young children and its rightward shift with time (Fig. 5).

JEV infection in pigs (see p. 151 of this issue)**:** PHIs have been testing pigs, an amplifier of JEV, that are brought to slaughterhouses during summer (5-8 months old). Emergence of JEV HI antibody positive pigs, i.e., primary infection rate among pigs of the corresponding year, has been used as an indicator of the JEV activity (Fig. 6). It usually starts in the South and progresses to the North. In recent years, the earliest detection of antibody-positive pigs has been around May in Okinawa and around July in other parts of Japan, all west of Toyama Prefecture.

In 2008, by the end of October, of the 35 prefectures that surveyed pig sera, there were 34 prefectures that detected JEV antibody-positive pigs, and 24 among them detected it in more than 50% of the pigs. In 2003-2008, the JE patients were found in the prefectures with higher incidence of antibody positive pigs (http://idsc.nih.go.jp/yosoku/index.html).

Virus isolation/detevtion: JEV was detected from one case in Hiroshima Prefecture in 2002 (genotype III), one case in Shizuoka Prefecture (genotype I), and one deceased case in Aichi Prefecture (genotype I). The majority of recent JEV isolates in Japan has been genotype I (see p. 153 of this issue). A JE virus detected from pigs in Ishigaki Island, Okinawa Prefecture in 2005 was genotype III and was close to isolates from Taiwan in 1985-1996 (see p. 155 of this issue). Isolation of JEVs from wild boars in Hyogo Prefecture in December 2008 and May 2009 (genotype I) suggested implication of wild boars as an amplifier of the agent (see p. 156 of this issue). It is important to continue the isolation/detection of JEV or its genome from patients, pigs, wild boars and mosquitoes for the purpose of surveillance of JEV.

Conclusion: The decrease of JE cases in recent years can be attributed to three factors, (1) the regular vaccination that gave sufficient protective immunity to children, (2) decreased population of mosquitoes due to decreased paddy fields and switch of cultivation method of rice to the one unfavorable for mosquito larvae (Kamimura, Med Entomol Zool 49 (3): 181-185, 1998); and (3) keeping pig farms away from residential areas.

In recent years, however, the JE epidemiology appears changing. While the elderly used to be the majority of the patients, recent JE occurred among children and middle-aged people, too. Some JE cases occurred in prefectures where no JE case had been reported. JE antibody positive pigs were detected in prefectures with no reported human JE cases. It is possible that infective mosquitoes are now present all over Japan from Okinawa to Hokkaido. JE should be always included in differential diagnoses of encephalitis or encephalopathy during summer.

On February 23, 2009, a new freeze-dry tissue culture JE vaccine was approved for production and sale. On March 19, the vaccination advisory board, MHLW, concluded that "recognizing persisting risk of JEV infection in Japan, the role played by vaccine is crucially important", and proposed preferential vaccination to children who have no JE immunity. Subsequently, on June 2, 2009, MHLW revised the Rules of Immunization Practice to the effect that the new vaccine is included in the first stage of the regular vaccination (see p. 157 of this issue).

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Control Division,
Ministry of Health, Labour and Welfare

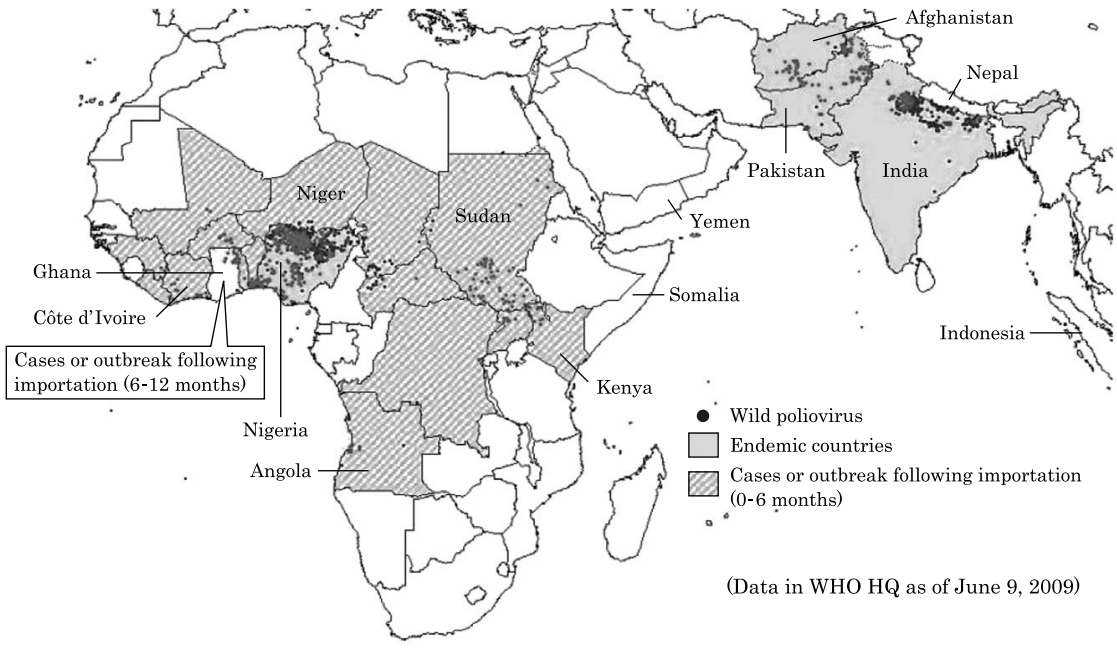
<THE TOPIC OF THIS MONTH>
Poliomyelitis as of 2009

Poliomyelitis, often called simply as polio or known as infantile paralysis, is caused by infection of the central nervous system by poliovirus. Typically, the infection irreversibly damages motor neurons causing acute flaccid paralysis (AFP). As no specific therapeutics is available, prevention by vaccination is the basic strategy against this disease. Polio is a notifiable category II infectious disease under the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (the Infectious Diseases Control Law), which obliges doctors who have diagnosed symptomatic or asymptomatic cases (excluding carriers of vaccine strain) to make immediate notification. Vaccine-associated paralytic poliomyelitis (VAPP) and poliomyelitis caused by secondary infection of vaccine strain excreted by vaccinees are included in the case definition for notification (see http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01.html). As AFP is produced by causes other than poliovirus, poliovirus isolation from stool specimens, identification and the genetic analysis of the isolates are the global standard for the surveillance of polio.

Present situation of the global polio eradication program

Since WHO launched the global polio eradication program in 1988, the total polio cases and endemic areas steadily decreased in number, and type 2 wild poliovirus has not been isolated since the last isolation in India in 1999. Now in 2009, the type 1 and type 3 wild polioviruses are circulating in four remaining polio endemic countries, Nigeria, India, Pakistan and Afghanistan (Fig. 1). The basic strategy adopted by WHO is to prevent transmission of the wild poliovirus by mass vaccination with the oral polio vaccine (OPV) that is cheap and easy to administer. Even now, in polio endemic areas and high-risk areas, extensive OPV campaign is being continued. In spite of these efforts, the program has not progressed significantly further since 2000, which was the WHO's target year of the eradication (Fig. 2). All the above four countries unable to eradicate polio have regional problems. In 2008-2009, India experienced increased incidence of type 3 wild polio in its northern states (WHO, WER

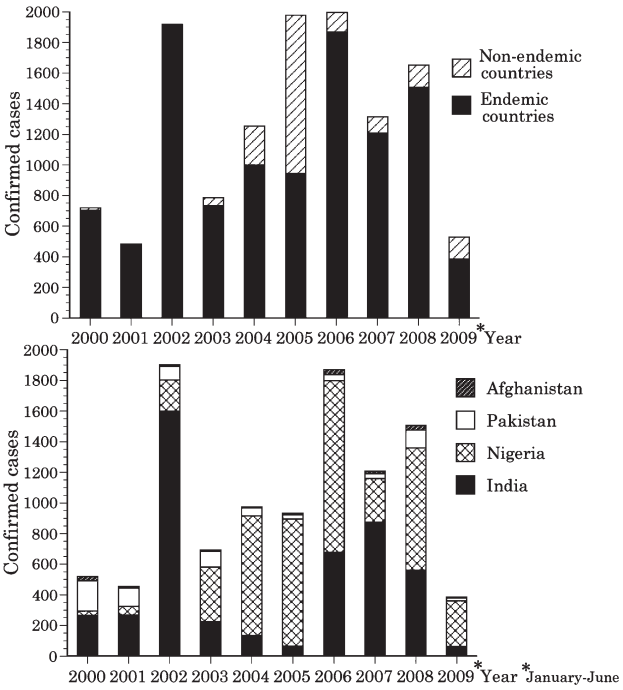
Figure 1. Distribution of the wild polio cases in the world, June 2008-June 2009



84: 110-116, 2009). In 2004-2005, type 1 wild polio originating in Nigeria spread to Sudan, Somalia, Yemen, Indonesia and other countries, resulting in a large-scale polio outbreaks. All these epidemics were brought under the control (Fig. 2). In 2008-2009, however, type 1 poliovirus originating in Nigeria spread to Niger, Cote d'Ivoire, Sudan, and Kenya, and type 1 and type 3 wild type polioviruses both originating in India spread to Nepal and Angola, respectively. Thus, exportation of wild type polio from endemic countries is now a big problem for global eradication of polio (WHO, WER 84: 110-116 & 133-140, 2009).

Since 2000, polio outbreak caused by vaccine-derived poliovirus (VDPV) has been reported from various parts of the world. In Nigeria, in particular, type 2 VDPV together with types 1 and 3 wild polioviruses has been circulating for these 4 years (see p. 174 of this issue). In the WHO Western Pacific Region (WPR), the wild polio ceased to be transmitted since 2000 when the termination of the wild poliovirus transmission was declared. However, small-scale VDPV outbreaks and imported wild polio cases have been reported. Therefore, potential of polio outbreak still persists in WPR (see p. 173 of this issue).

Figure 2. Confirmed cases of wild polio in 2000-2009



Top figure: Number of confirmed cases of wild polio in two categories of countries, endemic or non-endemic countries. The figures indicate total number of polio cases in either category of countries.
Bottom figure: Number of confirmed cases in each of the endemic countries (India, Nigeria, Pakistan and Afghanistan). (WHO, as of June 9, 2009)

Polio surveillance in Japan

In Japan, obligatory notification of polio cases under the Infectious Diseases Control Law and various surveillance activities under the National Epidemiological Surveillance of Vaccine-Preventable Diseases (NESVPD) ensure absence of importation and/or circulation of wild poliovirus and VDPV. In the polio infectious agent surveillance under NESVPD, poliovirus isolates from polio patients and healthy children have been analyzed every year. Since 1993, no wild poliovirus has been isolated in Japan (see p. 176 of this issue). The polio susceptibility surveillance conducted also under NESVPD confirmed antibody prevalence sufficient for preventing spread of wild polioviruses (see p. 178 of this issue). For introduction of inactivated polio vaccine (IPV), sensitive and accurate polio laboratory surveillance has to be continued. Development of new polio surveillance methodology including environmental surveillance needs to be considered (see p. 180 of this issue).

Laboratory diagnosis of poliovirus

The basic of the laboratory diagnosis is isolation and identification of poliovirus using cultured cells and intra-typic differentiation, differentiation of vaccine type and non-vaccine type viruses (wild poliovirus and VDPV). Increasing realization of risk caused by VDPV has necessitated laboratory diagnosis with higher precision, and presently isolates judged as non-vaccine-like polioviruses in the genetic or antigenic analysis are further submitted to nucleotide sequencing of the whole VP1 region. Isolates having mutations in 1% or more of the region are considered as VDPV that accumulated mutations through considerably long circulation. Once VDPV is detected, intensive surveillance should be conducted. If considered necessary, polio-preventing measures such as supplemental OPV vaccination campaign should be conducted.

After attaining the eradication of polio, poliovirus stocked in laboratories becomes the only source of polio epidemic. For that concern, the laboratories including those in Japan were investigated for their possession of poliovirus, and Japanese government submitted the quality assurance report attached with the list of laboratories possessing wild poliovirus to the Regional Commission for the Certification of Poliomyelitis Eradication in the Western Pacific (see p. 181 of this issue).

Issues to be considered

WHO places the global polio eradication program as the number one priority among infectious disease control programs, and is advancing policies optimizing the vaccination in the polio endemic countries. However, ending the circulation of wild poliovirus within coming few years is a hard challenge in the present circumstances. Considering that the polio eradication is not within reach in the immediate future, it is important to continue high quality polio surveillance even in polio free countries including Japan. So long as OPV is used, VAPP will be continuously reported and risk of polio epidemic caused by VDPV never disappears. Actually in Japan VAPP cases have been reported intermittently (0-2 cases/year, IASR 29: 200-201, 2008) and VDPV was detected (see p. 176 & 180 of this issue). Therefore, many countries are replacing OPV with IPV, and Japan also needs to take the same action immediately. The vaccine combining IPV and DPT being developed in Japan, when approved, can be used as vaccine replacing OPV and probably DPT also.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Enteric Infection in Japan, have provided the above data.

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National Institute of Infectious Diseases and
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Control Division,
Ministry of Health, Labour and Welfare

<THE TOPIC OF THIS MONTH>
Salmonellosis in Japan as of June 2009

Surveillance of salmonellosis in Japan is based on (1) notification of food poisoning cases in compliance with the Food Sanitation Law (compiled in "Statistics of Food Poisoning in Japan", Food Safety Division, Ministry of Health, Labour and Welfare; MHLW), and (2) report from prefectural and municipal public health institutes (PHIs) and health centers (HCs) on isolation of *Salmonella* from patients involved in food poisoning outbreaks (published in Infectious Agents Surveillance Report). The Department of Bacteriology, the National Institute of Infectious Diseases (NIID) conducts phage typing of isolates of *Salmonella enterica* subsp. *enterica* serovar Enteritidis (*S.* Enteritidis) as a part of the pathogen surveillance.

Under the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (Infectious Diseases Control Law), salmonellosis is included in the "infectious gastroenteritis", a category V infectious disease to be reported as such by sentinel points (pediatric clinics in this case). Therefore, under the National Epidemiological Surveillance of Infectious Diseases (NESID), the number of salmonellosis patients is not available.

1. Incidence of food poisoning according to Statistics of Food Poisoning in Japan

In 1999, 11,888 (43%) of 27,741 patients of bacterial food poisoning were caused by *Salmonella*. While having decreased significantly since 2000, 2,053 (21%), 3,603 (28%) and 2,551 (25%) salmonellosis were reported among 9,666, 12,964 and 10,331 patients of bacterial food poisoning in 2006, 2007 and 2008, respectively (see p. 206 of this issue and IASR 29: 213-215, 2008). *Salmonella* remains in the top two causative agents of bacterial food poisoning to this day. In 2006-2008, number of patients involved in one *Salmonella* food poisoning outbreak was, in average, 16.6, 28.6 and 25.8 in the respective three years. Outbreaks involving more than 500 patients are generally considered as large-scale outbreaks. In 2007, there was one such incidence, which was caused by *S.* Enteritidis-tainted catered lunch (see p. 207 of this issue). Food poisoning due to *Salmonella* has seasonal variation with its peak in July-September (Fig. 1).

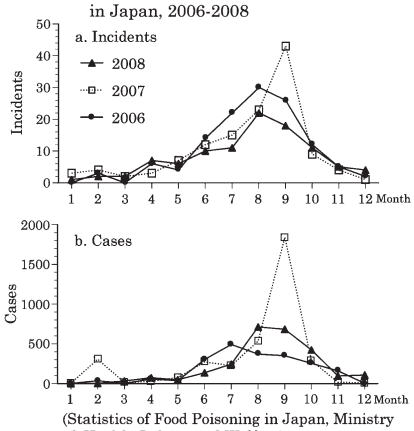
2. Laboratory findings in PHIs & HCs

1) Reports of *Salmonella* isolation: Until 1999, approximately 5,000 isolations of *Salmonella* were reported every year, but since 2000 the isolation number dropped significantly in parallel with the decrease of the *Salmonella* food poisoning. In 2006, 2007 and 2008, there were 1,104, 1,470 and 1,082 isolations (Fig. 2).

2) Serovars: There are more than 2,500 serovars in *Salmonella*. Among them, *S.* Enteritidis is the serovar most frequently isolated by PHIs and HCs from human specimens since 1989 (http://idsc.nih.go.jp/iasr/virus/bacteria-e.html). *S.* Enteritidis occupied 58% (3,830) of all the *Salmonella* isolates in 1996, but the percentage of *S.* Enteritidis among *Salmonella* isolates decreased gradually (Fig. 2), and in 2006-2008, it occupied 33% (360), 39% (576) and 32% (341) in respective years. As for *S.* Typhymurium that was isolated most frequently until 1988, there were 73 (6.6% of all the *Salmonella* isolates), 95 (6.5%) and 82 (7.6%) isolations in 2006, 2007 and 2008. As for *S.* Infantis that is frequently isolated from poultry, there were 67 (6.1%), 72 (4.9%) and 105 (9.7%) isolations in 2006, 2007 and 2008, respectively. As a consequence of the decrease in *S.* Enteritidis isolation (Fig. 2), other serovars are now becoming relatively frequent or even dominant in some areas, for example prevalence of *S.* Braenderup in Oita Prefecture (see p. 211 of this issue).

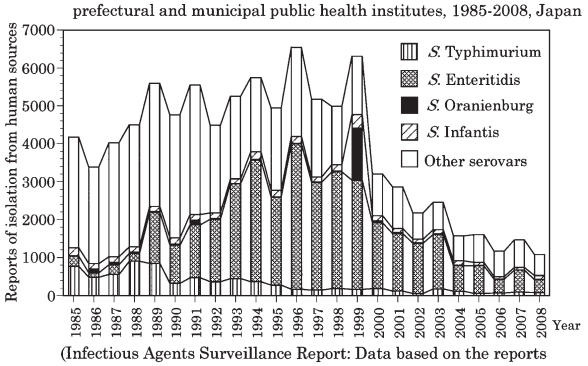
3) Outbreaks: Among outbreaks of salmonellosis reported by PHIs in 2006-2008, those involving more than 10 cases were 17, 20, and 25 in the respective years (Table 1). While there was a remarkable decline in the late 1990's to early 2000's, there has been no further decline in recent years (IASR 21: 162-163, 2000, 24: 179-180, 2003 and 27: 191-192, 2006). *S.* Enteritidis is the

Figure 1. Incidence of *Salmonella* food poisoning in Japan, 2006-2008



(Statistics of Food Poisoning in Japan, Ministry of Health, Labour and Welfare)

Figure 2. Yearly reports of *Salmonella* isolation from human sources at prefectural and municipal public health institutes, 1985-2008, Japan



(Infectious Agents Surveillance Report: Data based on the reports received before July 16, 2009)

Table 1. *Salmonella* serogroups and serovars associated with outbreaks involving 10 or more cases in Japan, 2006-2008

Year	O group	Serovar	Outbreaks	Suspected source	Place of consumption
2006 (17)	O4	Saintpaul	3	Catered lunch/Dishes served	Theater/Restaurant/Welfare facility
		Agona	1	Cooked and fried bean-curd refuse	Welfare facility
	O8	Newport	1	Unknown	Restaurant
	O9	Enteritidis	12	Tiramisu and other cakes/Lunches served/ Inari-sushi/Cooked fish/Freshly prepared Chinese cabbage	Nursery school/Kindergarten/Restaurant/Banquet/ Hotel/Work place/Home/Hospital
2007 (20)	O4	Saintpaul	2	Catered lunch/Dishes served	Restaurant/Banquet
	O7	Montevideo	1	Unknown	Restaurant
		Thompson	1	Processed meat	Restaurant
	O8	Not typed	1	Unknown	Welfare facility
	O9	Enteritidis	14	Roasted lobsters/Catered lunch/ Dishes served/ Egg soup/Omelet/Rolled omelet	Restaurant/Dormitory/Hospital/High school/Home for the elderly/Athletic ground/Home
		Not typed	1	Dishes served	Restaurant
2008 (25)	O4	Saintpaul	2	Dishes combined/Catered lunch	Home/Football stadium
		Typhimurium	1	Sashimi	Restaurant
		Not typed	1	Unknown	Boarding house
	O7	Infantis	3	Gratin with shrimp/Dishes combined	Restaurant/Hotel
		Braenderup	1	Boxed lunch	Junior high school
	O8	Yovokome	1	Processed meat	Restaurant
	O9	Enteritidis	16	Bowl of rice with cooked meat and egg on top/ Gomoku-sushi/Scrambled eggs/Dishes served/ Cooked spinach and mushroom/Cream puff	Restaurant/Funeral ceremony/Dormitory/School canteen/High school/Kindergarten/Hospital

( ): Number of outbreaks (Infectious Agents Surveillance Report: Data based on the reports received before July 16, 2009)

major serovar in the salmonellosis outbreak occupying 71% of the incidents in 2006, 70% in 2007, and 64% in 2008 (see IASR 28: 200-201, 300-301, 2007 and p. 209 & 210 of this issue). As for other serovars, *S.* Typhimurium caused one outbreak and *S.* Infantis caused three outbreaks in 2008. *S.* Saintpaul caused two or three outbreaks every year during 2006-2008.

As a rare case, soft-shelled turtles were incriminated in *S.* Typhimurium incidents in 2004 and 2007 (IASR 25: 261, 2004 and 29: 20-22, 2008).

Table 2. *S.* Enteritidis phage types associated with outbreaks, 2006-2008, Japan

Year	Outbreaks by phage type													Total outbreaks examined
	1	1c	3	4	5c	6	6a	14b	21	36	47	59	RDNC	
2006	7	–	1	7	2	1	9	8	2	1	4	1	4	47
2007	3	1	–	2	–	–	4	3	9	–	2	1	3	28
2008	4	–	–	2	–	–	1	11	3	–	1	–	–	22

Including familial infection, RDNC: Reaction does not conform.
(Department of Bacteriology, National Institute of Infectious Diseases: As of June 30, 2009)

3. Phage types (PT) of *S.* Enteritidis

Department of Bacteriology, NIID, has conducted phage typing of *S.* Enteritidis derived from outbreaks including familial ones (Table 2). PTs 1, 4, which were prevalent in 1990s, were continued to be isolated in 2006-2008. PT6a was most frequent in 2006, PT21 in 2007, and PT14b in 2008.

4. Salmonellosis in reptiles

In 2006-2008, there was no report of salmonellosis mediated by infected reptiles. However, public education on hygienic practices in raising such animals needs to be continued (see Notice of December 22, 2005 by the Tuberculosis and Infectious Diseases Control Division, MHLW), because, carrier rate of *Salmonella* is still significant among turtles in Japan (see p. 212 of this issue), and there was a multistate outbreak of turtle-mediated food poisoning in the USA in 2007 (MMWR 57: 69-72, 2008).

5. Conclusion and Comments

1) *Salmonella* food poisoning has decreased in recent years.

2) *S.* Enteritidis tends to cause serious systemic infection leading to death. In 2006, there was one such fatal case. Among 16 fatal cases of *Salmonella* infection encountered in 1996-2008, 14 were due to *S.* Enteritidis and 2 others were respectively due to *S.* Typhimurium and *S.* Haifa (see p. 206 of this issue). Patients with diarrhea accompanied by fever should consult physicians and receive appropriate treatment without delay (see p. 211 of this issue).

3) As hen's eggs are very frequently contaminated with *S.* Enteritidis, their handling needs special hygienic precaution. Special measures to prevent secondary infection from contaminated eggs and kitchen utensils should be taken. Handling of chicken meat needs caution as *Salmonella*-positive rate in chicken ground meat is still high (see p. 206 of this issue and Notice of March 30, 2009 by the Food Safety Division, MHLW). However, *Salmonella* contaminating the chicken meat is *S.* Infantis rather than *S.* Enteritidis, indicating that eggs and meat are infected through different routes.

4) In recent years, isolation of *Salmonella* serovars other than *S.* Enteritidis is becoming relatively frequent. Such serovars, e.g. *S.* Montevideo and *S.* Braenderup (IASR 29: 221-222, 2008 and see p. 211 of this issue), are often implicated in food poisoning whose source could not be identified in spite of geographical concentration of the patients.

5) Large-scale outbreaks were caused by fresh fruits and vegetables abroad (see p. 205 of this issue), and some such cases were caused by minor serovars, such as *S.* Tennessee and *S.* Saintpaul. An outbreak caused by *S.* Typhimurium-tainted peanut butter was reported in USA. Though some such butter was imported into Japan, adverse consequence was avoided by the prompt recall from the market upon information from the USA. In this case, pathogen information including genetic type shared among Japan and the USA facilitated the case investigation.

6) As food poisoning is globalizing, international information sharing on the food poisoning incidents and genetic data of causative agents is becoming more and more necessary from now. Such information sharing is now being facilitated through USA PulseNet and European CDC.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Enteric Infection in Japan, have provided the above data.

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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

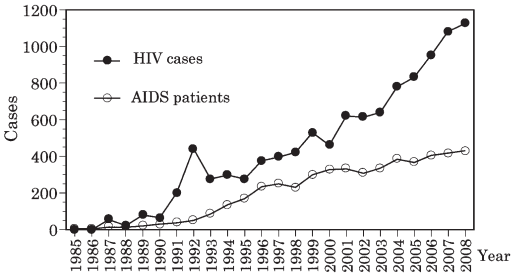
<THE TOPIC OF THIS MONTH>
HIV/AIDS in Japan, 2008

HIV/AIDS surveillance started in 1984. It was carried out in compliance with the AIDS Prevention Law from 1989 to March 1999, and, since April 1999, as part of the National Epidemiological Surveillance of Infectious Diseases (NESID), in accordance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections. The data presented below are derived from the final version (June 17, 2009) of the 2008 annual report of the National AIDS Surveillance Committee released by the Specific Disease Control Division, the Ministry of Health, Labour and Welfare (MHLW) (http://api-net.jfap.or.jp/htmls/frameset-03-02.html).

1. Trend in HIV/AIDS cases reported during 1985-2008: Cases reported in 2008 were 1,126 for HIV (1,059 males and 67 females) and 431 for AIDS (391 males and 40 females). The respective numbers for 2007 were 1,082 and 418, and the numbers for 2008 were the higher than ever (Fig. 1). In the AIDS surveillance, HIV is defined as the case that is detected by laboratory diagnosis before development of AIDS, and AIDS as the case detected by the manifest AIDS symptoms.

The cumulative number of HIV and that of AIDS (both excluding infections through the contaminated coagulation factor products) from 1985 to 2008 were 10,552 (8,590 males and 1,962 females) and 4,899 (4,307 males and 592 females), respectively. They were equivalent to the incidence of 8.259 and 3.834 per 100,000 population (calculated using population as of October 2007). The "nationwide survey of blood coagulation anomalies" conducted independently identified 1,439 HIV cases due to the contaminated coagulation factor products. That number includes 169 AIDS patients alive and 638 cases deceased (as of May 31, 2008).

Figure 1. HIV cases and AIDS patients, 1985-2008, Japan



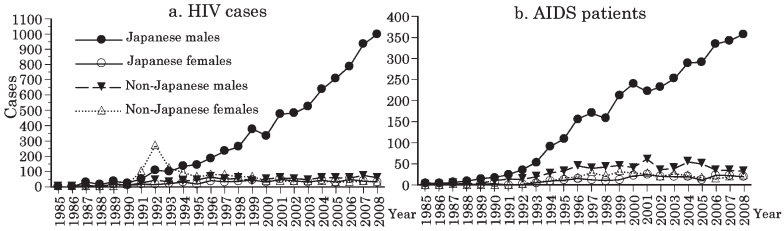
(The 2008 Annual Report on HIV/AIDS Surveillance in Japan, the National AIDS Surveillance Committee, Ministry of Health, Labour and Welfare)

Nationality and gender: HIV cases continue to increase among the males of the Japanese nationality. They numbered 999 in 2008 (931 in 2007) occupying 89% of all the HIV cases. The same tendency was observed for AIDS; there were 359 Japanese males in 2008 (343 in 2007) occupying 83% of the total AIDS. For males of non-Japanese nationality, however, the both HIV and AIDS tend to decrease. For females, HIV cases decreased among the both Japanese and non-Japanese nationalities (Fig. 2).

Infection route and age distribution: The most frequent infection route was homosexual (including bisexual) contact of males for these years. In 2008, it recorded the highest figures, 743 HIV (692 in 2007) and 182 AIDS (152 in 2007) (Fig. 3). Among this group, the 30s has been the most prominent in number and in the rate of increase, though it decreased slightly in 2008 (290 in contrast to 304 in 2007). The homosexual infections among 20s and 40s continued to increase. The increase of HIV among homosexuals in 50s was remarkable this year (49 in 2008 in contrast to 26 in 2007) (Fig. 4). As a consequence, the infection through homosexual contacts occupied 78% of all the HIV cases for population of 15-49 years and 52% for population of 50 years or older. The infection through heterosexual contacts was 14% for the former population and 28% for the latter population. For Japanese females, the common infection route is heterosexual contact.

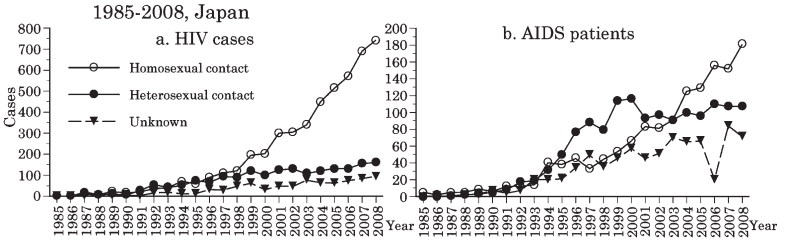
There were additional 10 cases of HIV infection through intravenous drug abuse (6 Japanese and 4 non-Japanese) and 6 cases categorized as "others" that include those who had chance of infection through drug abuse and sexual contacts. Infection through drug abuse is much less frequent in Japan than in other countries. There was no report of the mother-to-child infection in 2008.

Figure 2. Nationality and gender of HIV cases and AIDS patients, 1985-2008, Japan



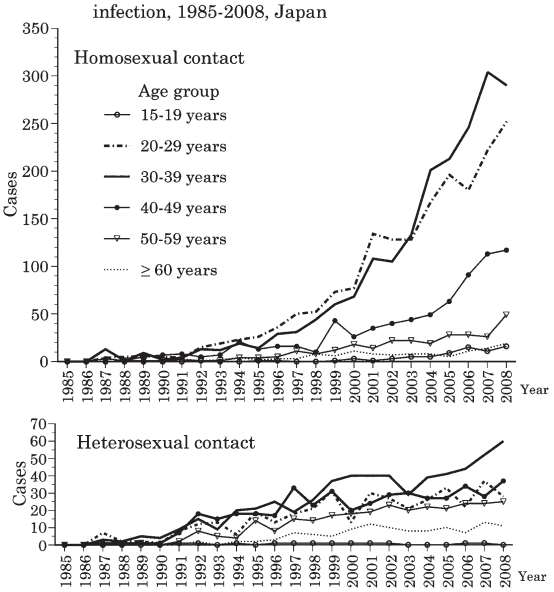
(The 2008 Annual Report on HIV/AIDS Surveillance in Japan, the National AIDS Surveillance Committee, Ministry of Health, Labour and Welfare)

Figure 3. Mode of infection of Japanese male HIV cases and AIDS patients, 1985-2008, Japan



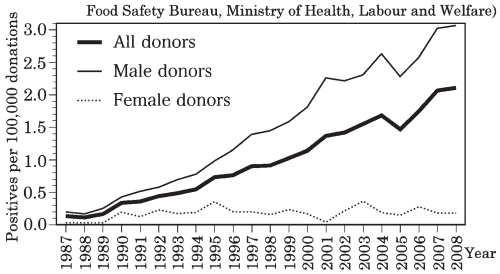
(The 2008 Annual Report on HIV/AIDS Surveillance in Japan, the National AIDS Surveillance Committee, Ministry of Health, Labour and Welfare)

Figure 4. Japanese male HIV cases by age group and mode of infection, 1985-2008, Japan



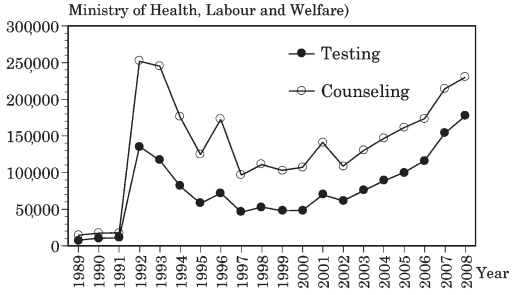
(The 2008 Annual Report on HIV/AIDS Surveillance in Japan, the National AIDS Surveillance Committee, Ministry of Health, Labour and Welfare)

Figure 5. HIV-antibody positives (by the confirmatory test) among blood donors in Japan, 1987-2008
(Blood and Blood Products Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)



In 2000, 2001, 2002, 2003, 2004, 2005, 2006 and 2007, three of 67, one of 79, two of 82, two of 87, two of 92, two of 78, one of 87, and six of 102 donors, respectively, were positive only by the nucleic acid amplification test.

Figure 6. HIV testing and counseling at health centers, 1989-2008
(Specific Disease Control Division, Health Service Bureau, Ministry of Health, Labour and Welfare)



Including other settings provided by municipalities

Place of infection: In 2008, 91% of HIV (92% for male and 85% for female) and 76% of AIDS (76% for male and 68% for female) were presumably infected in Japan. For non-Japanese males, since 2001, infection in Japan has been more frequent than infection outside of Japan.

Reports by districts: The prefectures reporting more than 10 HIV cases were, in the decreasing order, Tokyo, Osaka, Kanagawa, Aichi, Fukuoka, Hyogo, Saitama, Chiba, Shizuoka, Kyoto, Okinawa, Hokkaido, Hiroshima, Okayama, Ibaraki, Tochigi, and Gunma. The reports from Tokyo and Osaka respectively occupied 40% and 17% of all the reports. Among the regional blocks of prefectures, the Kanto/Koshin-etsu block that includes Tokyo reported 54%, and the Kinki block that includes Osaka reported 22% of all the reports. The number of reports increased from 2007 to 2008 in all the blocks except Hokkaido/Tohoku and Tokai blocks.

2. HIV-antibody-positive rates among blood donors: In 2008, there were 107 HIV-positives in 5,077,238 blood donations (104 males and 3 females), corresponding to 2.107 positives (3.065 for males and 0.178 for females) per 100,000 donations. This rate was higher than ever (2.065 in 2007) (Fig. 5).

3. HIV antibody tests and consultation provided by the local governments: The local governments are providing HIV antibody tests at health centers and at other facilities. They are increasingly utilized. Total number of HIV tests carried out by the local governments in 2008 was 177,156 (in contrast to 153,816 in 2007) (Fig. 6). The health center covered 146,880 tests, and the other facilities 30,276. The HIV antibody positive rate was 0.28% (501/153,816) as a whole. When looked at it by the facilities, the positive rate tended to be higher for the other facilities (0.64%, 194/30,276) than for the health centers (0.21%, 307/146,880). This difference is probably due to easier access to the other facilities. The number of counseling provided by the local governments increased from 214,347 in 2007 to 230,091 in 2008 (Fig. 6).

4. Drug sensitivities and subtypes of HIV: The frequency of the drug-resistant HIV carriers among those going to receive the chemotherapy for the first time is still low in Japan in comparison with Europe and North America. However, the tendency is towards the higher frequencies because it was 4.0% in 2003-2004, 7.8% in 2005, 6.6% in 2006 and 9.7% in 2007 (see p. 232 of this issue). As for prevalent HIV subtypes in Japan, there are three groups, subtype B transmitted among Japanese homosexuals, CRF01_AE transmitted through heterosexual contact among Japanese, and non-B subtype transmitted through heterosexual contact among non-Japanese (see p. 234 of this issue). HIV-2 infection that presumably occurred in Japan has been reported (see p. 235 of this issue).

Conclusion: The numbers of HIV and AIDS reported in 2008 were higher than ever, and the HIV-positives among the blood donors too. HIV transmission mainly through the homosexual contact is increasing continuously among all the age groups of the Japanese males (see p. 231 of this issue).

It is considered that the activities of the local governments during the World AIDS Day in December and the HIV Week for Promotion of HIV Testing in June (started in 2006) have greatly contributed to the increased number of HIV testing and counseling throughout the year. Nevertheless, the local and national governments are further requested to strengthen the public education on AIDS prevention and to promote HIV testing for earliest possible detection necessary for appropriate clinical intervention. They should consider possible collaboration with necessary partners, such as, educational and/or medical staff, companies, and NGOs while taking into account the target populations, such as, younger generations, foreigners, homosexuals, sexual workers and their clients, males whose behaviors are conductive to HIV infection, etc.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Enteric Infection in Japan, have provided the above data.

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<THE TOPIC OF THIS MONTH>
Pandemic (H1N1) 2009 in Japan, May-September 2009

Emergence of novel influenza: On April 12 2009, increase of deaths due to pneumonia and influenza-like illness (ILI) was reported from Mexico to World Health Organization (WHO) in compliance with the International Health Regulation. Subsequently, the virus isolates from Southern California, USA were found a novel influenza virus never isolated from humans and responsible for outbreaks in Mexico that started earlier. On April 24, WHO declared that the new influenza was a Public Health Event of International Concern. The virus spread in a short time to the rest of the world. WHO elevated the pandemic alert level to phase 4 on April 27, to phase 5 on April 29, and to phase 6 (the severity is moderate) on June 11.

The virus has had different names since its discovery, but now the WHO's official name is influenza A (H1N1)pdm (abbreviated as AH1pdm below), and the disease caused by it is called pandemic (H1N1) 2009.

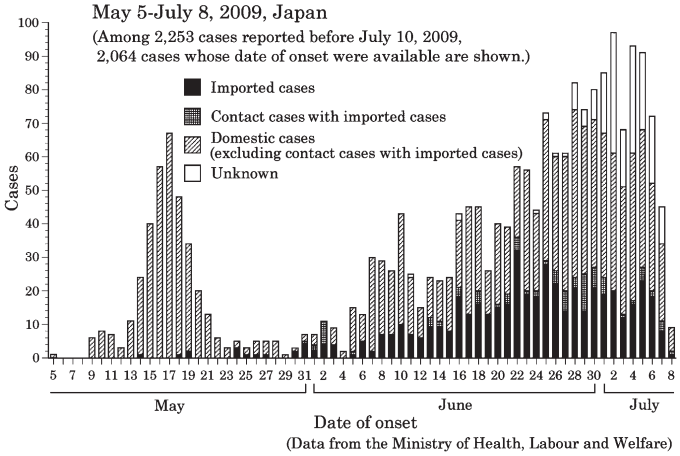
Start of the epidemic in Japan: On April 28, in response to elevation of the WHO pandemic alert level to phase 4, the pandemic (H1N1) 2009 was classed as "pandemic influenza and relevant infections" under the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (Infectious Diseases Control Law), and quarantine measures were enforced immediately. On May 9, three passengers including high school students coming back from Canada via USA were found infected with AH1pdm (see p. 257-258 of this issue). On May 16, the first domestic infection was found in Kobe City and Osaka Prefecture, which were probably epidemiologically unrelated. Further investigation revealed outbreaks in Osaka and Hyogo Prefectures mostly among high school students (see p. 266 of this issue). The immediate measures taken were to ask feverish patients to consult "fever consultation centers" first and then under the centers' guidance to visit "fever clinics", to isolate all the laboratory-confirmed cases in the designated hospitals, to close schools in the affected area temporarily, and to request close contacts to remain at home. Such measures were effective in preventing further local spread of the infection (see p. 259 of this issue). From mid June on, however, the pandemic influenza spread Japan wide (Fig. 1), and by July 16 no prefecture was left unaffected (see p. 260-265 of this issue).

Surveillance in Japan: In early phase of the epidemic, in compliance with the Infectious Diseases Control Law, laboratory diagnosis of all the suspected cases and notification of all the diagnosed influenza patients were norms. On July 24, however, after reporting of 5,038 confirmed cases, the norm was replaced by cluster surveillance (reports of outbreaks in various settings) and hospital admission surveillance for severe cases, in addition to routine sentinel surveillance, pathogen surveillance, school absentee surveillance (reports of school outbreak of ILI). At the same time, the law-based isolation of the patients in hospitals was discontinued.

Influenza sentinel surveillance in Japan that started in 1987 is based on weekly report of ILI from sentinel points (currently approximately 5,000 sentinels including 2,000 clinics of internal medicine and 3,000 clinics of pediatrics). About 10% of them are pathogen sentinels too. Specimens obtained in the pathogen sentinels and those obtained from outbreaks and serious cases were sent to the prefectural and municipal public health institutes (PHI) for virus isolation and identification. The isolates were then sent to National Institute of Infectious Diseases (NIID) and analyzed for antigenicity, genetic characterization, and drug susceptibility.

As all the feverish patients had to go to "fever clinics" initially, the number of influenza cases reported from influenza sentinels remained at a low level. But it started to increase from week 28 (July 6-12) when the "fever clinics" were discontinued and consultation of feverish patients was allowed in general clinics

Figure 1. Cases of pandemic influenza (H1N1) 2009 by date of onset, May 5-July 8, 2009, Japan



(Data from the Ministry of Health, Labour and Welfare)

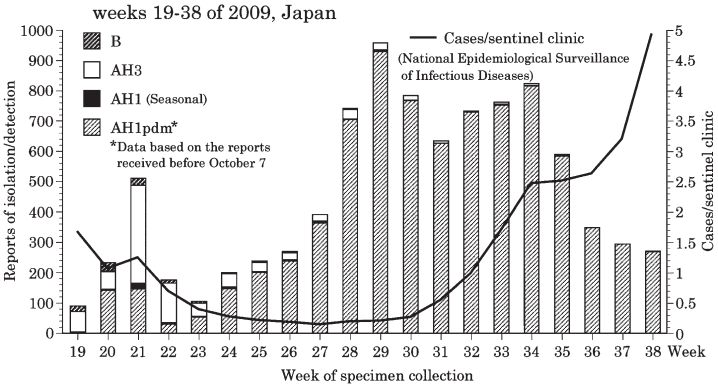
including sentinel clinics. The number of cases per sentinel reached 1.69 on week 33, far exceeding 1.00, an indicator of the start of an influenza epidemic. On week 38 (September 14-20), it reached 4.95 (Fig. 2) and the total number of the influenza patients who visited the medical facilities in this country in the week was estimated to be 270,000. In Okinawa Prefecture, the influenza patients increased sharply towards the end of July and attained 46.31 cases per sentinel at its peak in week 34 (see p. 264 of this issue).

In May when the AH1pdm virus was first isolated in Japan, subtype AH3 was dominant, but from week 24 (June 8-14) on, AH1pdm started to dominate, and, since July, almost all the influenza patients were infected by AH1pdm (Figs. 2&3 and http://idsc.nih.go.jp/iasr/influ-e.html).

Reports from school absentee surveillance and cluster surveillance indicated that temporary closures owing to the influenza outbreak were increasing among schools and other places in September after summer vacation.

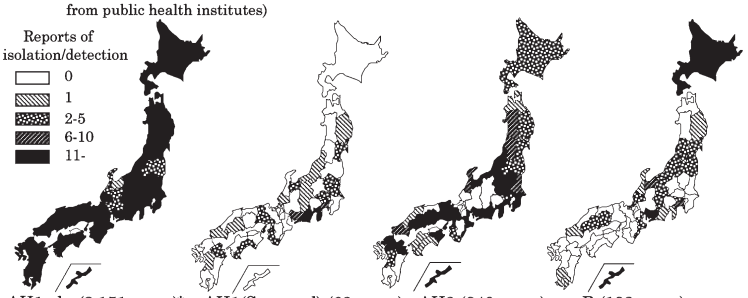
Symptoms and prognosis: The symptoms of pandemic (H1N1) 2009 are pharyngitis, sudden onset of high fever, cough, running nose and general fatigue, almost indistinguishable from those of the seasonal influenza (see p. 266 of this issue). The case-fatality rate calculated by using the Mexico outbreak data was 0.4-0.5%, which was equivalent to that of Asian flu and higher than that of the seasonal influenza 0.05%. People with ailments like asthma, diabetes, heart diseases, and decreased immunity occupied half of the fatal cases. Highly obese people and pregnant women in the third trimester are considered at high risk.

Figure 2. Weekly cases of influenza and isolation/detection of influenza viruses, weeks 19-38 of 2009, Japan



(Infectious Agents Surveillance Report: Data based on the reports received before October 6, 2009, from public health institutes)

Figure 3. Isolation/detection of influenza viruses by prefecture, weeks 19-38 of 2009, Japan
(Infectious Agents Surveillance Report: Data based on the reports received before October 6, 2009 from public health institutes)



*Data based on the reports received before October 7, 2009

Though the fatal case has been small in number in Japan yet, severe cases have increased with the increase of the patients; 54 patients needing artificial respirators (see p. 267 of this issue), 34 patients of acute encephalopathy (see p. 268 of this issue), and 17 fatalities among 1,323 hospitalized patients have been reported to the Ministry of Health Labour and Welfare (MHLW) as of September 29. While most fatal cases were adults, the majority of hospitalized patients were children. About 40% of the hospitalized patients had background ailments (http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/index.html).

Laboratory diagnosis: As early as May 1st, PHIs and major quarantine stations were ready to conduct PCR diagnosis of AH1pdm using primers and positive controls provided by NIID (the primers were designed by NIID using the data published by Center for Disease Control and Prevention, USA). It is important to note that the rapid diagnosis kit for antigen detection that is widely used in clinics in Japan cannot detect the antigen, including that of AH1pdm, during the onset of fever, but, on one day later, it detects the antigen-positives more efficiently.

Treatment: In Japan, antiviral drugs have been used for treatment of the influenza patients and they should not be used for prophylaxis in principle. Antiviral drug therapy can be started without the laboratory data. The viruses with H275Y mutation associated with oseltamivir resistance have been isolated in Denmark, Japan (see p. 270 of this issue), Hong Kong, USA, Mexico and other countries, but they have not posed clinical problems yet.

Vaccines: The influenza vaccines licensed in Japan are adjuvant-free, embryonated chicken egg-derived ones. After having produced 80% of the amount of the seasonal influenza virus vaccine prearranged for the 2009/10 influenza season, production was switched to pandemic influenza AH1pdm vaccine. The vaccine strain chosen was A/California/7/2009(H1N1)pdm-like recommended by WHO, and the production method was the same as that used for the seasonal influenza virus. The projected production scale is equivalent to 54,000,000 doses (or for 27,000,000 persons if each person receives two doses). The proposed vaccination targets are, in the order of priority, medical staff, pregnant women, persons with ailments, children from 1 year old to the 3rd grade of the primary school, and parents of 0-year-old children. If the vaccination targets are extended to all students at primary, secondary and high schools and to elderly, however, the domestic production may not be able to cope with the amount required. Adjuvant-combined vaccines and vaccines derived from tissue culture cell grown virus are produced in abroad.

Conclusion: As preparedness for the expansion of the epidemic, enforcement of surveillance, consolidation of the medical services, procurement of sufficient amount of therapeutics and vaccines are in immediate need. For assisting treatment of serious cases, the past experience with the influenza encephalopathy and experience of the respiratory control are placed on the MHLW website, http://www.mhlw.go.jp/kinkyu/kenkou/influenza/hourei.html.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Enteric Infection in Japan, have provided the above data.

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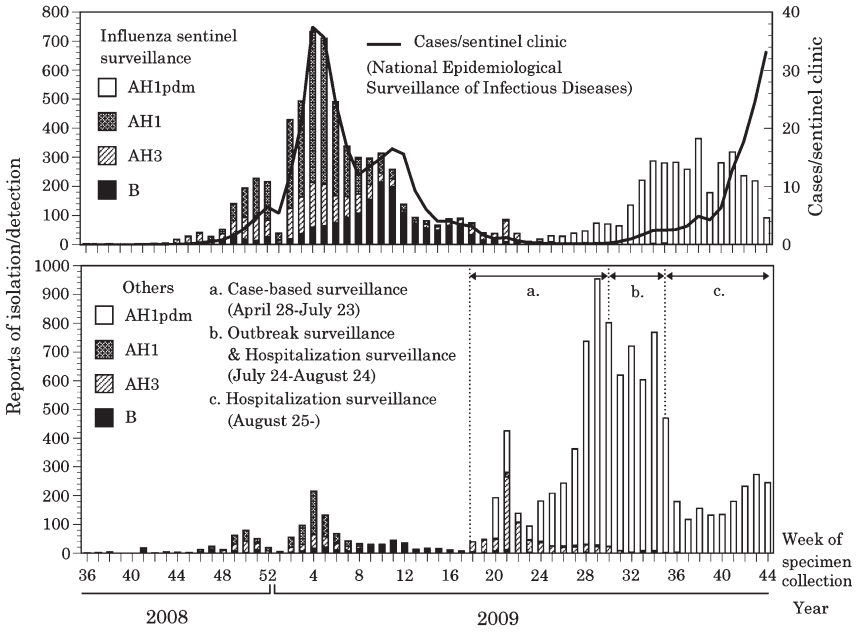
<THE TOPIC OF THIS MONTH>
2008/09 influenza season, Japan

In 2008/09 season, from week 36 of 2008 (September) to week 35 of 2009 (August), the first wave of influenza was caused by the seasonal influenza AH1 and AH3 and peaked towards the end of January 2009. The second wave was the seasonal influenza B in March and the third wave was the resurgence of AH3 in April-May. The pandemic (H1N1) 2009 started in May in Japan (IASR 30: 255-270, 2009).

Incidence of Influenza: Under the National Epidemiological Surveillance of Infectious Disease (NESID), the influenza sentinels (3,000 pediatric and 2,000 internal medicine clinics) weekly report the number of clinically diagnosed influenza cases. Weekly cases per sentinel on the nationwide level outnumbered 1.0, an indicator of the start of the influenza epidemic, in week 49 of 2008, peaked in week 4 of 2009 (37.5), subsided temporarily in weeks 6-8, peaked again in week 11 (16.5), and gradually decreased to less than 1.0 in week 22 (Fig. 1 and http://idsc.nih.go.jp/idwr/kanja/weeklygraph/01flu.html). As for pandemic (H1N1) 2009, the sentinel clinics started to report increasingly from week 28 when the local governments stopped "fever clinic" and cases/sentinel exceeded 1.0 again in week 33 (1.7). In the past 10 seasons, the peak incidence of this season was the third highest following the 2004/05 and 2002/03 seasons; the total number of cases per sentinel of this season (288.70) was the second highest following the 2004/05 season.

Hokkaido Prefecture experienced the first wave of influenza earlier than other prefectures (https://hasseidoko.mhlw.go.jp/Hasseidoko/Levelmap/flu/index.html). Okinawa Prefecture, where the influenza epidemic persisted till summer in the past four seasons, was attacked by the pandemic (H1N1) 2009 towards the end of July before termination of seasonal influenza (IASR 30: 264-265, 2009).

Figure 1. Weekly cases of influenza and isolation/detection of influenza viruses from week 36 of 2008 to week 44 of 2009, Japan



(Infectious Agents Surveillance Report: Data based on the reports received before November 4, 2009)

Table 1. Isolation of influenza viruses during 1999/2000-2008/09 seasons

Type	Isolates from specimens collected during September through August next year*									
	1999/2000	2000/01	2001/02	2002/03	2003/04	2004/05	2005/06	2006/07	2007/08	2008/09
AH1pdm	–	–	–	–	–	–	–	–	–	2,906 (5,277)
AH1	4,462 (23)	1,866 (25)	3,268 (14)	1	5	184	1,347 (28)	595 (38)	3,646 (173)	3,302 (300)
AH3	2,711 (11)	806 (5)	3,108 (21)	5,141 (31)	4,800 (47)	2,531 (33)	3,401 (27)	2,289 (107)	506 (38)	1,839 (763)
B	10	2,310 (107)	1,905 (5)	2,606 (20)	291 (2)	3,359 (41)	519 (10)	1,986 (55)	311 (19)	1,915 (122)
A (H subtype unknown)	–	–	1	1	–	– (1)	– (1)	–	–	– (8)
C	6 (4)	–	10 (1)	–	28 (4)	3	14 (9)	10	24	1 (1)
Total	7,189 (38)	4,982 (137)	8,292 (41)	7,749 (51)	5,124 (53)	6,077 (75)	5,281 (75)	4,880 (200)	4,487 (230)	9,963 (6,471)

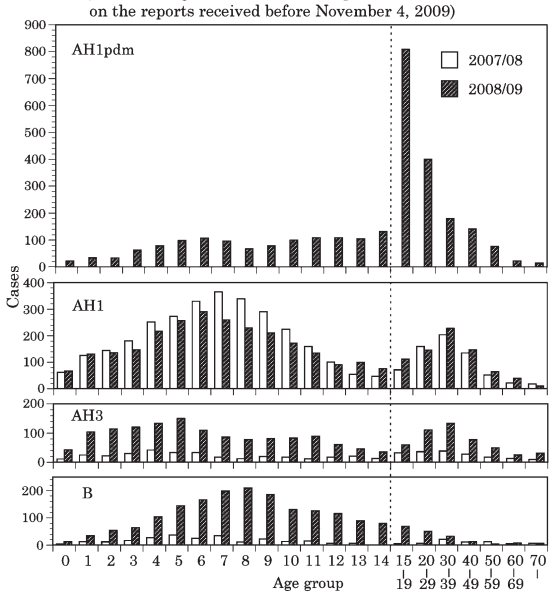
*Reports from prefectural and municipal public health institutes. ( ):Gene or antigen detection, not included in the total.
(Infectious Agents Surveillance Report: Data based on the reports received before November 4, 2009)

The number of influenza encephalopathy which is categorized as "acute encephalitis" (category V infectious disease that requires report of all the cases) reported by week 18 was total 53 (due to seasonal influenza; 42 for type A, 7 for type B, and 4 for type unknown). Between week 27 and 35, there were 14 additional reports (10 for AH1pdm, 3 for type A and 1 for type B).

Isolation/detection of influenza viruses: During 2008/09 season, the number of viruses detected by isolation by prefectural and municipal public health institutes (PHIs) was 9,963 (as of November 4, 2009, Table 1). The number of viruses detected by PCR alone was 6,471, in much larger number than usual, owing to the fact that PHIs took part in PCR differential diagnosis of AH1pdm since May. Among total 16,434 influenza virus isolation/ detection, those from specimens collected at non-sentinel clinics (8,838) exceeded those from specimens collected at influenza sentinel clinics (7,596) (Table 2 in p. 287 of this issue). From people who came back from abroad, not only AH1pdm (692) but also seasonal AH1 (39), AH3 (154), and type B (3) were isolated/detected.

From the start of 2008/09 season, AH3, B of Victoria lineage and AH1, all associated with outbreaks, were isolated one after another (IASR 29: 340-341, 2008). Oseltamivir resistance with H275Y mutation was initially found among AH1 isolates from Sendai City and Shiga Prefecture in October and in November, respectively (IASR 30: 47-49, 2009). The oseltamivir-resistant AH1 then became the majority of all the seasonal influenza viruses (IASR 30: 49-53, 2009). In 2008/09 season, 99% of AH1 isolates from Japan turned out to be oseltamivir-resistant (see p. 287 of this issue and IASR 30: 101-106, 2009).

Figure 2. Age distribution of cases with isolation of influenza virus in 2007/08 and 2008/09 seasons, Japan
(Infectious Agents Surveillance Report: Data based on the reports received before November 4, 2009)



AH3 and AH1 peaked at week 4 (Fig. 1), and AH3 peaked again at week 21 (IASR 30: 182-184, 2009). Type B peaked at week 10, and persisted till week 28 (Fig. 1 and http://idsc.nih.go.jp/iasr/prompt/graph-pke.html).

Isolation/detection of AH1pdm (first isolated in week 19) from the influenza sentinel clinics started to increase from week 32 (Fig. 1).

As for the age distribution (Fig. 2), AH1 that was dominant both in the preceding and this season had two peaks, one at the age of 6 among children and the other in the age of 30's among adults. AH3 increased in all ages from 2007/08 season. Influenza B was most frequently isolated from children with the peak at 8 years. AH1pdm was most frequently isolated from 15-19 year olds.

Antigenic characteristics of 2008/09 isolates: Among AH1 isolates, 94% obtained in the first half of the season and 85% obtained in the latter half of the season resembled A/Brisbane/59/2007 (the vaccine strain for 2008/09 season). As for AH3 isolates, 72% obtained in the first half of the season resembled A/Uruguay/716/2007 (the vaccine strain for 2008/09 season), but later than March, A/Perth/16/2009-like viruses with entirely different antigenicity occupied 75% of the isolates. For type B, Victoria-lineage viruses prevailed in 2008/09 season (75%). Victoria-lineage isolates were largely deviated from B/Malaysia/2506/2004 (the vaccine strain for 2006/07-2007/08 seasons) in their antigenicity. B/Yamagata-lineage isolates resembled B/Bangladesh/3333/2007 and showed antigenicity different from B/Florida/4/2006 (the vaccine strain for 2008/09 season). AH1pdm isolates were all similar to A/California/7/2009pdm (the vaccine strain for 2009) in their antigenicity (see p. 287 of this issue).

Seasonal vaccine strains selected for 2009/10 season: A/Brisbane/59/2007 and A/Uruguay/716/2007 were selected for AH1 and AH3, respectively (the same as for 2008/09 season). For B, selected was B/Brisbane/60/2008 belonging to the Victoria lineage (see p. 287 of this issue).

Vaccine production and immunization rate among the elderly: For 2008/09 season, 53,920,000 doses of the seasonal vaccine were produced, and 49,020,000 doses were used. The vaccination coverage among the elderly (primarily those aged 65 years or older defined by the Preventive Vaccination Law) was 56% in 2008/09 season (55% in 2007/08 season). For 2009/10 season, after having produced 45,040,000 doses of the seasonal vaccine, the production was switched to AH1pdm vaccine and 54,000,000 doses will be produced by March 2010. The immunization of AH1pdm vaccine started on October 19 targeting the medical staff first.

Conclusion: It is increasingly important to grasp the trends of both pandemic (H1N1) 2009 and seasonal influenza. Sentinel surveillance and infectious agent surveillance, both have been playing an important role in this respect, should be strengthened. Virus isolation should be conducted throughout the year, and possible antigenic, genomic and drug-sensitivity changes should be followed. These activities are crucial for detecting possible changes in the properties of the virus including its virulence and also for obtaining appropriate vaccine strains. Vaccine strain for AH1 recommended for 2010 in the Southern Hemisphere is A/California/7/2009pdm in place of the seasonal influenza (WHO, WER 84: 421-432, 2009).

Data obtained for 2009/10 season, preliminary report (http://idsc.nih.go.jp/iasr/influ-e.html)**:** AH1pdm are continuously reported in large numbers. AH3 was isolated/detected from 7 cases in Fukuoka, Hokkaido, Saitama, Shizuoka and Wakayama Prefectures in weeks 36-39 (see p. 297 of this issue), but there have been no reports of influenza B and AH1 since week 29 and week 36 respectively (as of November 10, 2009).

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Enteric Infection in Japan, have provided the above data.

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<THE TOPIC OF THIS MONTH>
Shigellosis, Japan, 2006-2009

It is estimated that in Asia, 91 million people have shigellosis every year, and 414,000 among them, mostly malnourished children, die of this infection (WHO, WER 80: 94-99, 2005). *Shigella* spp. is classified into four serogroups, *S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei*. *S. dysenteriae* serovar 1 (Sd1) is particularly pathogenic as it produces the neurotoxigenic and cytotoxigenic Shiga toxin closely related to the toxin produced by enterohemorrhagic *Escherichia coli*. It has been experimentally shown that as few as tens to hundreds *Shigella* bacteria can cause infection (Morris, 1986).

The amendment of the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (the Infectious Diseases Control Law) in December 2006 brought shigellosis together with cholera, typhoid and paratyphoid fever from category II to category III infectious disease from April 2007 (IASR 28: 185-188, 2007). Consequently physicians no longer need to report suspected cases. Admission of the patients to hospitals based on advice was repealed (http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-03-02.html).

The amendment in 1999 of Food Sanitation Law Enforcement Regulation added *Shigella* to the list of etiological agents of food poisoning. Number of food poisoning incidents caused by *Shigella* reported in compliance with the law was eight in 2000-2005 (182 patients) (IASR 27: 61-63, 2006), one in 2006 (10 patients) (IASR 27: 340-341, 2006), zero in 2007, and four in 2008 (140 patients) (IASR 29: 342-343, 2008). All the incidents involved restaurants.

The Infectious Diseases Control Law was amended in November 2003 (IASR 24: 328-329, 2003) to the effect that, since October 2004, veterinarians are under obligation to report *Shigella*-infected monkeys immediately to the nearby health center when they find them. From 2005 to 2009, 30-50 infected monkeys were reported every year and 193 monkeys in total (see p. 317 of this issue).

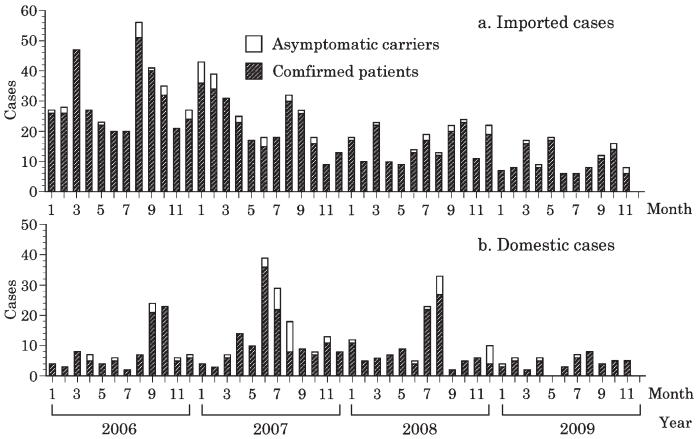
Trends in notified cases: According to the National Epidemiological Surveillance of Infectious Diseases (NESID), the number of reported cases of shigellosis was 477 in 2006, 452 in 2007, 318 in 2008, 166 in 2009 (as of November 18), and 1,413 in total from 2006 to now (excluding 11 and 2 suspected cases reported in 2006 and January-March 2007, respectively).

As reported previously (IASR 27: 63, 2006), most of the suspected places of infection are abroad, particularly Asian countries, which are India, Indonesia (see p. 314 of this issue), China (IASR 28: 326-327, 2007), Viet Nam, Cambodia and Thailand, in the order of frequency (Table 1 in page 313). Infections in August-October had previously been the majority. However, since 2008, the number of infection abroad decreased throughout the year, and the seasonal curve became flat (Fig. 1a).

The domestic infections remained in rather low level throughout the year (Fig. 1b) though there were outbreaks in September-October 2006 (involving a restaurant in Ishikawa Prefecture, IASR 27: 340-341, 2006, and a nursery school in Osaka Prefecture, IASR 28: 45-46, 2007), in June-August 2007 (involving a welfare facility for the retarded in Saitama Prefecture, IASR 30: 99-100, 2009, a college in Tokyo Metropolis and nursery schools in Hiroshima and Shizuoka Prefectures), and in July-August 2008 (involving restaurants in Fukuoka Prefecture, IASR 29: 342-343, 2008). In 2009, no domestic outbreaks have been reported so far (as of December 10, 2009).

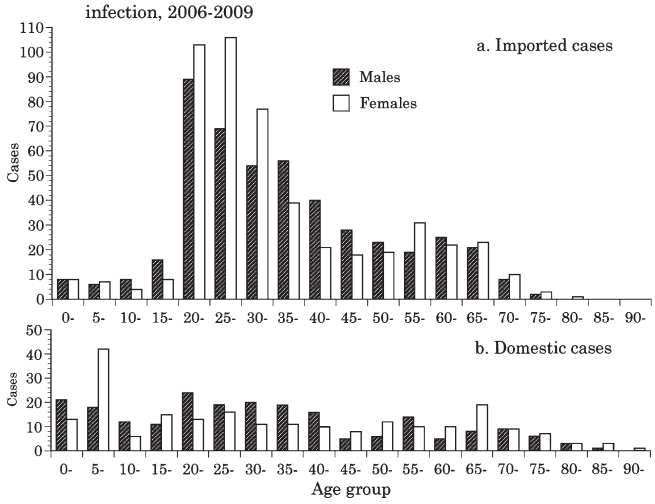
During 2006-2009, among those infected abroad, young adults aged 20-29 were the large majority (Fig. 2a), and in the age group of 20-34 years, significantly more females were affected than the males. Among those infected domestically, the incidence among 5-9 years of age tended to be high, which was due to outbreaks in the nursery schools in 2006 and 2007 (Fig. 2b). Total 691 males and 722 females had shigellosis in 2006-2009.

Figure 1. Monthly cases of shigellosis, by suspected region of infection, 2006-2009



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before November 18, 2009)

Figure 2. Age distribution of shigellosis cases, by gender and suspected region of infection, 2006-2009



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before November 18, 2009)

Table 2. Yearly reports of *Shigella* isolation, 2000-2009

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Prefectural and municipal public health institutes										
Shigella dysenteriae	4 (4)	2 (1)	2 (2)	2 (2)	3 (2)	1 (1)	3 (3)	1 (1)	1 (1)	–
Shigella flexneri	45 (16)	40 (12)	66 (8)	21 (5)	40 (20)	33 (20)	34 (19)	17 (2)	36 (16)	6 (4)
Shigella boydii	4 (4)	2 (1)	3 (1)	8 (5)	2 (2)	3 (1)	1	1 (1)	11 (11)	–
Shigella sonnei	205 (77)	225 (55)	186 (47)	79 (43)	101 (72)	66 (38)	91 (48)	165 (59)	103 (40)	31 (18)
Shigella spp. UT	–	1 (1)	–	–	–	4 (3)	–	–	–	1 (1)
Quarantine stations										
Shigella dysenteriae	8 (8)	1 (1)	1 (1)	4 (4)	4 (4)	–	2 (2)	1 (1)	–	–
Shigella flexneri	42 (42)	33 (33)	26 (26)	22 (22)	18 (18)	21 (21)	14 (14)	3 (3)	–	–
Shigella boydii	5 (5)	6 (6)	5 (5)	6 (6)	8 (8)	7 (7)	2 (2)	–	–	–
Shigella sonnei	189 (189)	181 (181)	125 (125)	120 (120)	162 (162)	146 (146)	127 (127)	74 (74)	–	–
Shigella spp. UT	–	–	1 (1)	–	–	–	–	–	–	–

UT: Untypable, ( ): Imported cases included in the total
(Infectious Agents Surveillance Report: Data based on the reports received before November 17, 2009)

Table 3. Examination of *Shigella* from imported foods

Fiscal year	Number of examined	Number of positives	Total weight (t) of foods examined
2007	211	0	114
2008	331	0	799
2009	14	0	114
Total	556	0	1,028

*Data for 2009 as of November 2, 2009

Isolation of *Shigella*: Frequency distribution of serogroups reported by prefectural and municipal public health institutes (PHIs) in 2006-2008 remained unchanged, 68-90% for *S. sonnei* and 9-26% for *S. flexneri* (Table 2). Among isolates of *S. flexneri,* serovar 2a was a majority (34/87). *S. dysenteriae* was isolated from five cases, but no Sd1 was isolated. *S. boydii* was isolated from 13 cases, eight of which were serovar 4.

Until 2006, *Shigella* reported from the quarantine stations was similar in number as from the PHIs. After cessation of laboratory diagnosis of diarrhea at quarantine stations since June 2007 (as a consequence of removal of cholera from the list of quarantine infectious diseases), there were no reports of *Shigella* from the quarantine stations since 2008 (Table 2).

Drug resistance: Strains resistant to tetracycline, ampicillin, sulfamethoxazole-trimethoprim, or nalidixic acid emerged in many countries, but ciprofloxacin (CPFX) and norfloxacin of fluoroquinolones are still effective. Japan Medical Association's guidelines recommend administration for 5 days of either of the fluoroquinolones and fosfomycin.

In recent years, *S. dysenteriae* and *S. flexneri* resistant to CPFX are increasing in India, Bangladesh and other East Asian countries (Taneja, 2007). The epidemiological trend of CPFX-resistant Sd1 should be closely watched. Since 2006, *S. sonnei* producing extended-spectrum β-lactamase (ESBL) has been isolated from imported cases (IASR 27: 264-265, 2006 and see p. 316 of this issue) and from outbreaks among those who never traveled abroad (IASR 28: 45-46, 2007).

Control of imported foods: A national food inspection plan is made every year based on the inspection data of imported foods and past cases of Food Sanitation Law breaches. Depending upon the size of the risk, monitoring by the quarantines is intensified or the importers are ordered to examine all the suspected foods before importation.

In October 2007, on information from abroad, monitoring for *Shigella* of young corns produced in Thailand was intensified (till August 2008). In response to the outbreak of food poisoning presumably caused by *Shigella*-contaminated frozen squids in Fukuoka City in July 2008 (IASR 29: 342-343, 2008), the importers were ordered in August 2008 to conduct microbiological examination of the Vietnamese marine products exported by the implicated exporter, and the quarantine stations intensified monitoring of all Vietnamese marine products.

Though *Shigella* has not been detected so far through the inspection (Table 3), the continued enforcement of the inspection capacity in the quarantine stations is necessary because not a few food poisonings in Japan were suspected to be caused by imported foods.

Problems and required measures: Most cases of shigellosis in Japan in recent years are infections abroad, secondary infections from the patients primarily infected abroad, or infections from imported foods. In an outbreak of college students infected abroad, many of them continued food handling job (IASR 28: 326-327, 2007). It is important to promote public education on imported infectious diseases. Travelers coming back from abroad should realize the importance of consulting quarantine stations or health centers when they have suspicious symptoms.

The number of *Shigella* bacteria isolated by PHIs and health centers is decreasing year by year when it is compared with the number of notified cases from clinics (only 150 isolations in contrast to 318 clinical cases in 2008). From September 2004, according to the amended Infectious Disease Control Law Enforcement Regulation, the health centers have power to request bacterial isolates from clinical institutions or from commercial laboratories when they receive reports of shigellosis. In the investigation of infectious diseases and food poisonings, it is important to obtain and analyze information on the genetic characteristics and drug sensitivity of the bacteria isolated from the patients (see p. 319 of this issue). It helps planning of the medical services, prediction of spreading pattern of the infection (e.g. wide-ranged or sporadic), identification of possible infection sources, and prevention of further spread. The health centers are encouraged to collect the isolates from clinics and commercial laboratories and send them to PHIs and the National Institute of Infectious Diseases (IASR 29: 314-315, 2008).

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